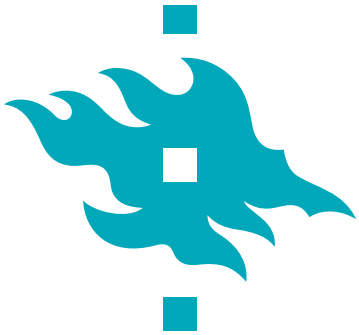

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JOHANNA JOKELA

SIALENDOSCOPY IN THE TREATMENT OF SALIVARY GLAND DISEASES

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HELSINKI UNIVERSITY HOSPITAL
FACULTY OF MEDICINE
DOCTORAL PROGRAMME IN CLINICAL RESEARCH
UNIVERSITY OF HELSINKI

Department of Otorhinolaryngology – Head and Neck Surgery
Helsinki University Hospital, and

Doctoral Programme in Clinical Research
Faculty of Medicine
University of Helsinki

Helsinki, Finland

SIALENDOSCOPY IN THE TREATMENT OF SALIVARY GLAND DISEASES

Johanna Jokela

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Supervised by
Riitta Saarinen, MD, PhD
Department of Otorhinolaryngology – Head and Neck Surgery
University of Helsinki and Helsinki University Hospital
Helsinki, Finland

Professor Antti Mäkitie, MD, PhD
Department of Otorhinolaryngology – Head and Neck Surgery
University of Helsinki and Helsinki University Hospital
Helsinki, Finland

Reviewed by
Docent Jura Numminen, MD, PhD
Department of Otorhinolaryngology
Tampere University Hospital
Tampere, Finland

Docent Tero Soukka, DDS, PhD
Department of Oral and Maxillofacial Diseases
Turku University Hospital
Turku, Finland

Opponent
Professor Francis Marchal, MD, PhD
Department of Otolaryngology – Head and Neck Surgery
University of Geneva
Geneva, Switzerland

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, which are referred to in the text by Roman numerals I–V:

I Jokela J, Haapaniemi A, Ojala J, Mäkitie A, Saarinen R. Sialendoscopy in sialadenitis: An unselected cohort of 228 patients. *Clin Otolaryngol*. 41:416–420, 2016.

II Jokela J, Haapaniemi A, Mäkitie A, Saarinen R. Sialendoscopy under local anaesthesia. *Acta Otolaryngol*. 137:310–314, 2017.

III Jokela J, Haapaniemi A, Mäkitie A, Saarinen R. Sialendoscopy in treatment of adult chronic recurrent parotitis without sialolithiasis. *Eur Arch Otorhinolaryngol*. 275:775–781, 2018.

IV Jokela J, Tapiovaara L, Lundberg M, Haapaniemi A, Bäck L, Saarinen R. A prospective observational study of complications in 140 sialendoscopies. *Otolaryngol Head Neck Surg*. 159:650–655, 2018.

V Jokela J, Saarinen R, Mäkitie A, Sintonen H, Roine R. Costs of sialendoscopy and impact on health-related quality of life. *Eur Arch Otorhinolaryngol*. 276:233–241, 2019.

ABBREVIATIONS

ASA	American Society of Anesthesiologists
CBCT	Cone beam computed tomography
CCI	Charlson Comorbidity Index
COSS	Chronic Obstructive Sialadenitis Symptoms
CSS	Chronic sclerosing sialadenitis
CT	Computed tomography
ESWL	Extracorporeal shock wave lithotripsy
GA	General anesthesia
GBI	Glasgow Benefit Inventory
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HUS	Helsinki University Hospital
IgG4-RD	Immunoglobulin G4-related disease
JRP	Juvenile recurrent parotitis
LA	Local anesthesia
LAS	Local anesthesia with sedation
MR	Magnetic resonance
MRI	Magnetic resonance imaging
NCSP	Nordic Classification of Surgical Procedures
NSAID	Nonsteroidal anti-inflammatory drug
OHIP-14	Oral Health Impact Profile-14
QoL	Quality of life
RAI	Radioiodine
SASDS	Sialendoscopy-assisted salivary duct surgery
SD	Standard deviation
SF-36	Short-Form-36 Health Survey
SS	Sjögren's syndrome
US	Ultrasound
VAS	Visual analogue scale
WHO	World Health Organization
15D HRQoL	15-dimensional health-related quality of life

ABSTRACT

During the last few decades, the treatment of sialolithiasis and chronic recurrent sialadenitis has shifted more toward a minimally invasive approach. The development of salivary endoscopy (sialendoscopy) has allowed visual access into the salivary duct system to diagnose and treat various duct conditions. Favorable results have been achieved in the treatment of sialolithiasis and duct strictures, and the symptoms of chronic sialadenitis seem to respond to this novel intervention as well.

The aim of the present study was to assess the results of sialendoscopy in the treatment of obstructive and chronic sialadenitis, the complications of sialendoscopy, and tolerability of sialendoscopy under local anesthesia (LA). In addition, the health-related quality of life (HRQoL) of sialadenitis patients and the costs of treatment were investigated.

We evaluated the medical records of all (n=228) patients who underwent sialendoscopy at the Department of Otorhinolaryngology – Head and Neck Surgery at Helsinki University Hospital (HUS) between January 2011 and December 2013. Using these data, we analyzed the main endoscopic findings and treatment results.

To assess the patient experience and compliance in sialendoscopy, 89 LA patients completed a questionnaire designed by the authors; on it, the patients rated their sensations (pain, discomfort, and nervousness) before, during, and after the operation using a scale from “none” to “major”.

In the prospective study, 49 patients with chronic recurrent parotitis without sialoliths were collected. They underwent sialendoscopy and were randomized to receive either a concurrent intraductal injection of isotonic saline solution or 125 mg of hydrocortisone (1:1).

To evaluate the incidence and nature of complications associated with sialendoscopy, we prospectively recruited 118 patients with 140 sialendoscopies between October 2015 and December 2016. Patient data, treatment failures, and complications were recorded in a database and analyzed.

In the fifth study, all patients (n=260) who had a sialendoscopy at our institution between January 2014 and May 2016 were identified from a surgical database, and the direct hospital costs were retrospectively evaluated from one year before to one year after the sialendoscopy. In addition, the 15D health-related quality of life (15D HRQoL) questionnaire and a survey exploring the use of health care services during the preceding three months were mailed to the patients preoperatively and at 3 and 12 months postoperatively.

The sialoliths were successfully removed in a majority of patients, but removal was possible with the endoscopic technique only in a minority. The symptoms resolved or improved in most patients after successful sialolith removal or stricture dilatation. Improvement was also seen in patients with inflammatory changes, but the symptoms relapsed quite often in this group. A single-dose steroid injection concomitant to sialendoscopy provided no additional benefit for the symptoms of chronic recurrent parotitis in this study.

In most cases, both diagnostic and interventional sialendoscopy were well tolerated under LA or under local anesthesia with sedation (LAS), with reasonably low patient-reported discomfort and pain. The complications of sialendoscopy were usually related to interventional procedures, and infection was the most common complication. Treatment costs were higher in sialolithiasis patients than in patients with other diagnoses. In sialolithiasis patients, the improvement of HRQoL was noticed at three months postoperatively.

In conclusion, according to this study, sialolithiasis patients benefit from the sialendoscopic intervention but combined techniques are often needed. Symptoms of chronic recurrent parotitis seem to improve after sialendoscopy, but total resolution of symptoms remains rare. Sialendoscopy is a safe and well-tolerated procedure, but not free of complications. It improves HRQoL, at least in patients with sialolithiasis in a short-term fashion.

SUMMARY IN FINNISH

Viimeisen parin vuosikymmenen aikana sylkikivitaudin ja kroonisen sylkirauhastulehduksen hoito on muuttunut vähemmän invasiiviseksi ja käyttöön on tullut nk. elimen säästävä hoito. Tähystysinstrumenttien kehityksen myötä hyvänlaatuisten sylkirauhasvaivojen diagnostiikka on tarkentunut ja tiehyttukosten hoito mahdollistunut. Hyviä tuloksia on saavutettu niin sylkikivien kuin tiehytahtaumienkin hoidossa. Myös kroonisen sylkirauhastulehduksen oireet lievittyvät usein ainakin väliaikaisesti sylkirauhasen tähystyksen myötä.

Tämän väitöskirjatyön tarkoituksena oli selvittää sylkirauhasen tähystyksen hoidollisia tuloksia ahtauttavan ja kroonisen sylkirauhastulehduksen osalta, tarkastella tähystykseen liittyviä komplikaatioita ja toimenpiteen siedettävyyttä paikallispuudutuksessa. Lisäksi tutkittiin potilaiden elämänlaatua ja sylkikivitaudin sekä sylkirauhastulehduksen hoitokustannuksia.

Kaikkien 1/2011-12/2013 Helsingin yliopistollisessa sairaalassa korva-, nenä- ja kurkkutautien poliklinikalla sylkirauhasen tähystyksessä olleiden potilaiden (228 potilasta) sairauskertomustiedot analysoitiin. Pääasialliset tähystyslöydökset ja hoitotulokset rekisteröitiin.

Kahdeksankymmentäyhdeksän potilasta, joille sylkirauhasen tähystys tehtiin paikallispuudutuksessa tai kevyessä sedaatiossa, täyttivät kyselykaavakkeen, jossa arvioitiin toimenpiteen aiheuttamaa kipua ja epämukavuutta.

Etenevään tutkimukseen kerättiin 49 kroonisesta, toistuvasta korvasylkirauhastulehduksesta kärsivää potilasta. Heille tehtiin sylkirauhasen tähystys ja potilaat satunnaistettiin saamaan tähystyksen yhteydessä tiehyeen sisäisesti annosteltua isotonista keittosuolaliuosta tai 125mg hydrokortisonia (1:1).

Toiseen etenevään tutkimukseen rekrytoitiin 118 potilasta, joille tehtiin yhteensä 140 sylkirauhasen tähystystä tutkimusaikana 10/2015-12/2016. Potilastiedot, epäonnistuneet toimenpiteet ja komplikaatiot rekisteröitiin.

Viidennessä osatyössä kaikkien potilaiden, joille oli tehty klinikassamme sylkirauhasen tähystys 1/2014-5/2016, sairaskertomustiedot haettiin potilasrekisteristä ja potilaiden hoitokustannukset selvitettiin kahden vuoden ajalta (vuosi ennen tähystystä ja vuosi tähystyksen jälkeen). Lisäksi 15D-elämänlaatukysely ja kysely käytetyistä sairaalapalveluista postitettiin potilaille ennen toimenpidettä sekä kolmen ja 12 kuukauden kuluttua toimenpiteestä.

Sylkikivet saatiin poistettua onnistuneesti suurimmalta osalta potilaista (77-84%), mutta ainoastaan pienellä osalla potilaista (12-23%) tämä onnistui pelkästään tähystimen ja kori-instrumentin avulla ilman tiehyeen avaamista. Oireet vähenivät tai parantuivat valtaosalla potilaista onnistuneen sylkikiven

poiston (95%) sekä tiehytahtauman avaamisen (79%) jälkeen. Myös potilailla, joilla löydöksenä oli tiehyen tulehdusmuutoksia, oireet helpottivat, mutta uusivat kohtuullisen usein (38%). Tiehyeen sisäisestä, tähystyksen yhteydessä annostellusta kortisoniannoksesta ei ollut lisäapua.

Sylkirauhasen tähystys todettiin tutkimuksessamme varsin hyvin siedetyksi toimenpiteeksi sekä paikallispuudutuksessa että kevyessä sedaatiossa tehtynä. Tutkimuksessa esiin tulleet komplikaatiot liittyivät yleensä tähystykseen, jossa tehtiin samalla hoitotoimenpide ja bakteeritulehdus oli yleisimmin havaittu komplikaatio. Hoitokustannukset olivat korkeammat sylkikivipotilailla muihin potilaisiin verrattuna. Sylkikivipotilaiden elämänlaatu parani 15D-kyselyn perusteella toimenpiteen jälkeen ainakin lyhyellä aikavälillä.

1 INTRODUCTION

Obstructive sialadenitis is the most common non-neoplastic condition of the major salivary glands. Obstruction decreases saliva flow with various sequelae and, for example, predisposes to bacterial infections. The symptoms are usually unilateral recurrent painful swelling exacerbated during meals, and the submandibular gland is the most frequently affected site (Butt 2012). The main cause of obstruction is sialolithiasis followed by strictures and stenosis (Nahlieli et al. 2006a, Ngy et al. 2007). Chronic inflammation is more common in the parotid gland. The inflamed gland is swollen and soreness might occur. Juvenile recurrent parotitis occurs in children, while Sjögren's syndrome and some other autoimmune diseases may cause inflammation and swelling of the salivary glands in adults. The etiology of sialadenitis often remains unknown (Motamed et al. 2003, Butt 2012).

Traditionally, symptomatic ductal or hilar stones have been managed by transoral incision and extirpation, while intraparenchymal and non-palpable stones have required removal of the gland. Treatment of chronic sialadenitis has been challenging when the conservative methods with nonsteroidal anti-inflammatory drugs (NSAID), gland massage, and hydration have failed. Ductal ligation and intraductal administration of different medicines have been attempted to induce atrophy of the affected gland (Bowling et al. 1994, Wang et al. 1998). Tympanic neurectomy has been used for the treatment of chronic recurrent parotitis with variable results, while sialadenectomy has been the last treatment option (Motamed et al. 2003).

Development of sialendoscopy throughout the 1990s and early 2000s has allowed the intraluminal visualization of the ductal system, permitting precise diagnostics, and minimally invasive treatment of salivary stones and strictures with a high success rate (Nahlieli & Baruchin 2000, Marchal et al. 2002, Koch et al. 2012a). There is also evidence that sialendoscopy can relieve the symptoms of chronic sialadenitis by flushing the mucus plugs and dilating the duct (Vashishta & Gillespie 2013) and even enhancing salivary flow and reducing xerostomia (Karagozoglu et al. 2018). In recent years, the use of sialendoscopy has spread worldwide, and meanwhile, the rate of sialadenectomies performed because of sialadenitis has reduced (Rasmussen et al. 2016). Sialendoscopy has been considered a safe and well-tolerated procedure. However, while the complications are usually minor, they still may necessitate re-operations or hospitalization.

During the last decade, greater interest has focused on the patients' health-related quality of life (HRQoL). Chronic recurrent sialadenitis causes symptoms that can continue for years or even decades and that are typically quite disruptive.

Thus, it could be assumed that the patients' HRQoL is decreased, but only a very limited amount of information exists in the literature. HRQoL can be measured either with generic or disease-specific questionnaires. The lack of a validated, sensitive questionnaire to assess the salivary gland-related quality of life has recently been recognized (Gillespie et al. 2015, Aubin-Pouliot et al. 2016b).

Although several case series and retrospective studies represent the efficacy of sialendoscopy in the treatment of obstructive sialadenitis, many procedure-related issues and guidelines still warrant further examination. The aim of the present study was to assess treatment outcomes of sialadenitis and sialolithiasis with sialendoscopy, to evaluate patient compliance and complications related to this technique as well as HRQoL of the treated patients and, further, to understand the costs related to the treatment of sialadenitis using a sialendoscopic approach.

2 REVIEW OF THE LITERATURE

2.1 Salivary glands

Human major salivary glands include the pairs of parotid, submandibular, and sublingual glands. Together, they are responsible for over 90% of the total saliva production. Additionally, about 600 to 1000 minor salivary glands locate throughout the oral cavity and pharynx within the submucosa. The main task of the salivary glands is to secrete saliva, which plays an important role in digestion and taste, the lubrication of food and buccal mucosa, immunity, and oral health (Holsinger & Bui 2007). The topographical location of major salivary glands is seen in Figure 1.

2.1.1 Embryology

The embryologic development of the salivary glands begins at six to eight weeks when oral ectodermal outpouching extends into the adjacent mesoderm. Important interactions between epithelial and mesenchymal tissues occur, controlling salivary gland morphogenesis. At the first stage, branched duct buds emerge due to repeated epithelial bud and cleft formation as a solid proliferation of bud-like structures invaginate toward a mesenchyme. At the second stage, the early lobules and duct canalization occur. Finally, the acini and intercalated ducts mature and the interstitial connective tissue decreases. The glands are extensively branched, showing differentiated terminal acinar buds, myoepithelial cells, and distinct ductal segments. The process is called branching morphogenesis and is also seen in the development of other secretory organs such as the lungs, pancreas, and kidneys. A capsule forms from ambient mesenchyme (Holsinger & Bui 2007, Varner & Nelson 2014, de Paula et al. 2017).

2.1.2 Anatomy

2.1.2.1 Parotid gland

The parotid glands are the largest salivary glands in humans, weighing on average 15 to 30 g. They are located in the preauricular region and along the posterior surface of the mandible. The facial nerve emerges from the stylomastoid foramen of the skull and enters the parotid gland at its posterior margin. It branches approximately 1.3 cm from the foramen and dives into the upper and lower division, which give rise to temporal, zygomatic, buccal, marginal mandibular, and cervical branches. The facial nerve divides the parotid gland into the superficial lobe overlying the masseter muscle and the deep lobe extending into

the parapharyngeal space. The superficial layer of deep cervical fascia splits to cover the parotid gland (Holsinger & Bui 2007).

Stensen's duct is the main excretory duct of the parotid gland. It arises from the anterior aspect of the gland, travels parallel to the zygoma over the masseter muscle, pierces the buccinator, and opens in the mouth at the level of the second upper molar tooth. It is about 5 cm in length and 0.5–1.4 mm in diameter. While the ostium is the narrowest part, the masseteric bend at the anterior border of the masseter muscle can be challenging to navigate during sialendoscopy (Zenk et al. 1998, Horsburgh & Massoud 2013).

The blood supply to the parotid gland comes from the branches of the external carotid artery, the superficial temporal and maxillary artery, and venous drainage is through the retromandibular vein. The secretory parasympathetic innervation of the parotid gland originates from the inferior salivatory nucleus and travels with the glossopharyngeal nerve, and via the tympanic nerve, synapsing in the otic ganglion with the lesser petrosal nerve and forming the auriculotemporal nerve, which carries parasympathetic fibers to the parotid gland. The facial nerve also supplies some secretory innervation to the parotid gland via the chorda tympani nerve. The sympathetic innervation originates from the superior cervical ganglion through the external carotid plexus. The sensory innervation is provided by the auriculotemporal nerve deriving from the mandibular branch of the trigeminal nerve (Holsinger & Bui 2007).

2.1.2.2 Submandibular gland

The submandibular glands are the second-largest pair of human salivary glands, weighing 7 to 16 g. They are located in submandibular triangles. The gland is divided into the superficial and deep lobes by the posterior edge of the mylohyoid muscle. Most of the gland lies caudally to the mylohyoid muscle. The deep part lies mostly on the mylohyoid muscle and posteriorly comes to contact with the hyoglossus muscle and the lingual and hypoglossal nerves. A capsule originating from the middle layer of the deep cervical fascia encloses the gland (Holsinger & Bui 2007).

The submandibular duct arises from the superficial lobe curving over the posterior edge of the mylohyoid muscle into the sublingual space where it runs as the Wharton's duct beneath the mucosa of the floor of the mouth, crosses the lingual nerve superiorly, and opens at each side of the lingual frenulum. It is approximately 5–6 cm in length and has a diameter of 0.5–1.5 mm (Zenk et al. 1998, de Paula et al. 2017).

The submandibular gland receives its blood supply from the lingual and facial arteries via sublingual and submental arteries, and the venous drainage is mainly

though the sublingual and submental veins, which drain into the lingual and facial veins, respectively (Holsinger & Bui 2007). Parasympathetic innervation to the submandibular gland is provided by the superior salivatory nucleus via the chorda tympani, a branch of the facial nerve, which synapses with the lingual nerve on the submandibular ganglion. The sympathetic innervation originates from the superior cervical ganglion (Holsinger & Bui 2007).

2.1.2.3 Sublingual gland

The sublingual glands are the smallest of the major salivary glands, weighing 2 to 4 g. They locate anteriorly in the submucosa, superficial to the mylohyoid muscle, and they lack the capsule. The secretion is excreted by several small sublingual ducts, referred to as the ducts of Rivinus, which open directly into the floor of the mouth, and via duct of Bartholin, which usually fuse with the Wharton's duct (Holsinger & Bui 2007).

As in the submandibular gland, the blood supply to the sublingual gland comes from the sublingual and submental arteries, and the venous drainage is through the sublingual and submental veins. Parasympathetic innervation originates from the superior salivatory nucleus and travels the same path as in the case of the submandibular gland. Sympathetic innervation is provided from the superior cervical ganglion (Holsinger & Bui 2007).

2.1.2.4 Minor salivary glands

Minor salivary glands are located throughout the oral and oropharyngeal submucosa, mostly in the buccal, labial, palatal, and lingual regions. They are 1 to 2 mm in diameter and are not encapsulated by connective tissue. Each gland has its own duct, which opens directly into the oral cavity. Parasympathetic innervation comes mostly from the lingual nerve and partly from the palatine nerve (Holsinger & Bui 2007).

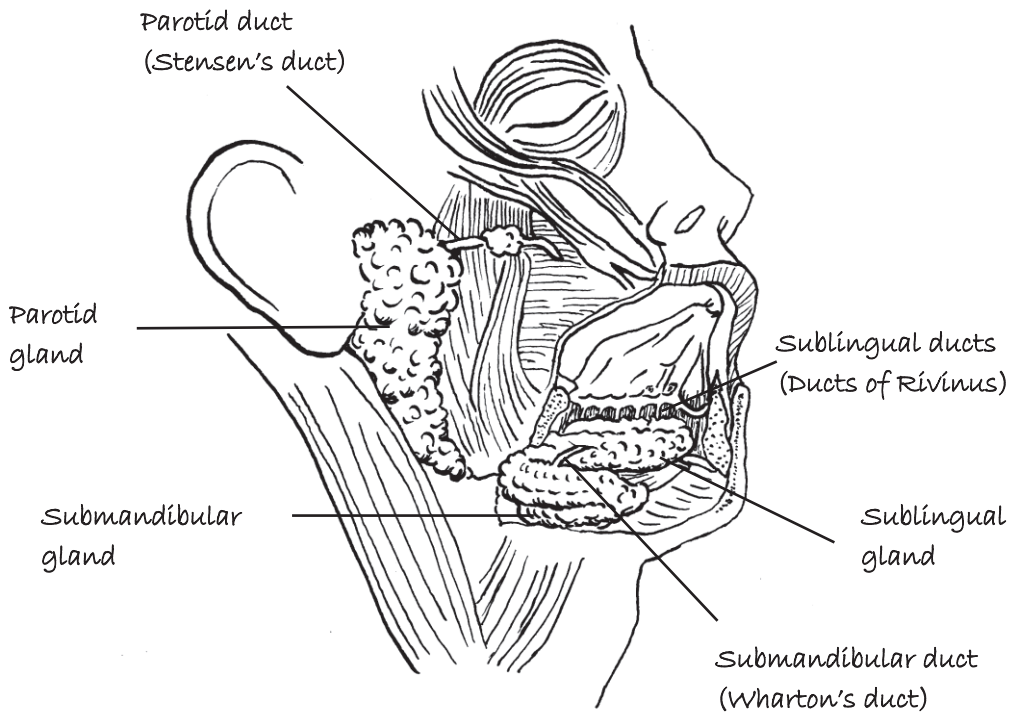

Figure 1 Anatomy of major salivary glands. Artist: Elina Romppanen.

2.1.3 Physiology

Salivary glands are composed of acini, the secretory units that drain into intercalated, striated, and excretory ducts. Myoepithelial cells surround the acini and intercalated ducts to support saliva secretion. The surrounding connective tissue divides the gland into the lobules. Three types of acini are recognized: serous acini secreting watery saliva; mucous acini secreting viscous, mucus saliva; and mixed or seromucous acini, which contain components of both types. The parotid glands are exclusively formed by serous acini and are responsible for about 25% of unstimulated saliva production, but during stimulation, their role increases and they supply about two-thirds of saliva secretion. Submandibular glands, which produce about 70% of unstimulated saliva, have mixed acini, but the serous ones predominate, unlike in the sublingual gland. The rest of the unstimulated saliva is produced by sublingual glands with mixed acini and minor salivary glands with solely mucous acini, producing 3–4% and 1–5% of saliva flow, respectively (Holsinger & Bui 2007, Elluru 2010).

A healthy adult secretes approximately 1.0–1.5 liters of saliva each day. The salivary production and secretion are under the control of complex neuronal signals by the autonomic nervous system. In general, parasympathetic

stimulation promotes the secretion of saliva with large volume and low protein contents, whereas sympathetic stimulation leads to the secretion of low volumes with higher protein contents. The ductal system actively participates in modifying the electrolyte concentration of saliva from isotonic primary saliva to a highly hypotonic solution and the flow rate influence for the electrolyte composition. Saliva is composed mainly of water, but it also contains other compounds such as electrolytes and mucins as well as enzymes and antimicrobial agents such as amylase, lipase, trypsin, lysozymes, peroxidases, lactoferrin, kallikreins, and immunoglobulin A. Saliva serves as a lubricant to facilitate speech, mastication, and swallowing, initiates food digestion, plays an important role in the sense of taste by carrying chemicals to the taste receptors, protects the teeth and oral mucosa, buffers the oral pH, and contributes to the remineralization of teeth (Elluru 2010).

2.2 Infectious diseases of the salivary glands

2.2.1 Acute suppurative sialadenitis

Although bacterial infection may involve any of the major salivary glands, the parotid gland is most commonly affected, probably due to serous saliva produced in the parotid glands, which has a smaller amount of the protective components such as IgA antibodies, sialic acids, lysozymes, and mucins when compared to mucous saliva of submandibular or sublingual glands (Rogers & McCaffrey 2010).

Acute suppurative sialadenitis presents with sudden pain and swelling, localized erythema, and tenderness of the affected gland and is usually unilateral. Purulent exudate from the duct is confronted, and the patient might have a fever (Peel & Seethala 2007, Rogers & McCaffrey 2010). Acute suppurative sialadenitis is usually caused by retrograde bacterial contamination of the salivary duct by oral flora. The stasis of salivary flow secondary to dehydration, post-surgical setting, radiation, anticholinergic medications, age or mechanical obstruction (e.g., sialoliths, strictures, or foreign bodies such as pieces of hair, fish bone, or food fragment) may allow bacterial migration into the gland. Also, diseases such as diabetes mellitus, periodontal disease, hypothyroidism, renal failure, and immunosuppression for any reason may predispose to acute sialadenitis (Peel & Seethala 2007, Brook 2002, Rogers & McCaffrey 2010). The hematogenic spread of bacteria or the transition from adjacent infection focus are rare causes (Scoggins et al. 2010).

The most common bacteria cultured in acute sialadenitis is *Staphylococcus aureus* (Raad et al. 1990, Brook 2002). *Streptococcal* species and *Haemophilus*

influenzae are also seen. The major role of anaerobic bacteria such as *Peptostreptococcus spp.* and anaerobic gram-negative bacilli (i.e., *Prevotella, Porphyromonas,* and *Fusobacterium spp*) have been recognized more recently, and they can be found in over half the cases. Mixed infections are common (Brook 2002). An evident-based review suggests that cephalosporins and fluoroquinolones display superior pharmacokinetics in saliva and cover most of the bacteria presented in sialadenitis, while phenoxymethylpenicillin and tetracyclines are not secreted in the saliva at bactericidal levels. Metronidazole may be a viable option in the management of anaerobes sialadenitis (Troeltzsch et al. 2014). Rarely, the condition can lead to abscess formation when surgical drainage might be necessary (Tan & Goh 2007).

2.2.2 Viral infections of the salivary glands

Viral sialadenitis most commonly spreads through hematogenous dissemination and is part of systemic disease. Typically, patients experience prodromal symptoms like malaise, low-grade fever, sore throat, headache, myalgia, and loss of appetite a few days before glandular symptoms. Glandular swelling and tenderness are usually bilateral, and there is no purulent discharge from the duct (McQuone 1999).

Mumps has been the most common cause of acute non-suppurative parotitis in children and adolescents until the 1990s. Since then, widespread vaccination has resulted in a more than 90% decline in rates of disease. The disease is highly contagious and spreads through aerosol droplets from saliva and nasopharyngeal secretions. Parotitis is present in about 60–70% of patients and in 95% of patients with symptoms (Hviid et al. 2008).

Several other viruses, such as Epstein-Barr virus, parainfluenza virus, influenza virus, Coxsackievirus, adenovirus, enterovirus, parvovirus, and human herpesvirus 6, have been related to parotitis with symptoms similar to those seen in mumps (McQuone 1999). In a study of 601 Finnish children and adolescents with mumps-like symptoms, the viral etiology was demonstrated in 84 (14%) patients (Davidkin et al. 2005). However, many of these viruses can also be detected in the saliva of asymptomatic persons.

2.2.3 Human immunodeficiency virus (HIV)–related parotitis

The most common salivary gland presentation among HIV-infected patients is painless and usually bilateral salivary gland swelling or enlargement. The prevalence is from 1–10% in HIV-positive individuals. Parotid glands are most often affected, and the state is usually secondary to the development of benign lymphoepithelial cysts. This condition is so unusual in the HIV-negative

population that cystic enlargement of the parotid glands should evoke suspicion of HIV infection, especially in children (Dave et al. 2007, Shanti & Aziz 2009). Swelling might also be related to diffusing infiltrative lymphocytosis syndrome, benign lymphoepithelial lesions, generalized lymphadenopathy, acute infections, or tumors such as lymphoma or Kaposi sarcoma in HIV-positive patients (Dave et al. 2007, Islam et al. 2012).

2.3 Obstructive sialadenitis

Obstructive sialadenitis is the most common benign inflammatory disease of the major salivary glands, usually presenting in the submandibular gland with unilateral recurrent painful swelling exacerbated during meals and sometimes complicated by bacterial infection (Butt 2012). Sialoliths are the main cause of obstructive sialadenitis, representing approximately 60–80% of all cases, occurring most often in submandibular glands. Strictures and stenosis are the second most common cause, contributing up to 15–25% of cases, and occurring more often in the parotid gland (Nahlieli et al. 2006a, Ngy et al. 2007, Gallo et al. 2016). It has been suggested that in patients with swelling of unclear origin, strictures may produce over 50–80% of cases (Koch et al. 2005, Vashishta & Gillespie 2013). Strictures and stenosis might be related to surgical manipulation of the ductal system or sialoliths, but they might also be due to chronic inflammation, e.g., autoimmune diseases, chronic recurrent parotitis, radioiodine treatment, or radiotherapy (Baurmash 2004, Koch et al. 2012b, Kopec et al. 2013b).

Other causes of obstructive symptoms include mucus plugs, polyps, foreign bodies, external pressure due to tumors, and congenital anomalies of the duct (Nahlieli et al. 2006a). The first-line treatment for acute symptoms of obstructive sialadenitis are NSAIDs, hydration, and antibiotics in cases of suppurative sialadenitis. Massaging the swollen gland with pressure from the fingers along the duct is beneficial since it will enhance the flow of saliva and decrease the swelling and pain.

2.3.1 Sialolithiasis

Postmortem studies have shown the prevalence of sialolithiasis to be up to 1.2% in the general population (Rauch & Gorlin 1970). Although small stones may not cause symptoms, the incidence of symptomatic sialolithiasis has been estimated to be between 1 in 10 000–30 000 individuals per year (Escudier & McGurk 1999, Marchal & Dulguerov 2003, Schroder et al. 2015). About 80% of salivary stones occur in submandibular glands and about 20% in parotid glands. Sialoliths in sublingual and minor salivary glands are very rare (Huoh & Eisele 2011, Zenk et

al. 2012, Sigismund et al. 2015). At the time of diagnosis, the average size of submandibular sialoliths has been reported to be about 8.3 mm (range 1–35 mm) and parotid sialoliths about 6.4 mm (range 1–31 mm) (Sigismund et al. 2015), with an annual growth rate of about 1 mm per year (Rauch & Gorlin 1970).

The peak incidence of sialolithiasis is between 30 to 60 years of age and remains rare in the pediatric population (Lustmann et al. 1990). Male predominance in the patient population has been reported before, but more recent studies report an equal distribution between men and women (Zenk et al. 2012, Schroder et al. 2015, Sigismund et al. 2015).

2.3.1.1 Pathophysiology and etiology

Sialoliths consist of varying ratios of organic and inorganic material. Although a few sialoliths are made up of only organic material, the majority of them are mainly composed of inorganic materials with an organic matrix arranged in a multilayer structure, including, e.g., calcium carbonates and phosphates, cellular debris, glycoproteins, and mucopolysaccharides (Grases et al. 2003, Rakesh et al. 2014).

The exact pathogenesis of sialolithiasis remains unknown, but various theories have been proposed. These hypotheses include the accumulation of microliths, retrograde migration of substances from the oral cavity, anatomical variations of the salivary ducts (Kraaij et al. 2014), and an altered biochemical composition of saliva (Grases et al. 2003, Demirhan et al. 2017). It has been suggested that age and secretory inactivity of the salivary gland may lead to increased formation of microliths, which gives rise to focal obstructive atrophy of the gland parenchyma and contributes to sialolith formation (Epivatianos et al. 1987, Harrison 2009). Other investigators have proposed that food debris and bacteria within the oral cavity may migrate into the salivary duct and serve as a nidus for stone formation. This process might be facilitated by variations in the sphincter-like mechanism (Nahlieli & Baruchin 2000, Marchal et al. 2001c, Chuangqi et al. 2013). This theory has been supported by studies that have found bacterial gene fragments in salivary calculi with a polymerase chain reaction, suggesting that the bacteria might have a potential role in the pathogenesis of sialoliths (Teymoortash et al. 2002, Fusconi et al. 2016). The longer course of Wharton's duct and the flow against gravity and the more viscous saliva with higher calcium concentration and alkaline pH may favor the formation of sialoliths in the submandibular glands (Kraaij et al. 2014). In general, it is thought that salivary stasis and inflammation contribute to the development of salivary stones (Harrison 2009). Proposed etiological factors include tobacco smoking, dehydration, the use of diuretics (Huoh & Eisele 2011), poor oral hygiene (Hung

et al. 2016), and hard water (Schroder et al. 2015), but their role remains controversial (Kraaij et al. 2015).

2.3.1.2 Treatment

The treatment of salivary stones depends on their size, shape, and location (Luers et al. 2011, Zenk et al. 2012). The primary goal should be the removal of the stone and preservation of the glandular function. Scintigraphic studies have shown that recovery of the secretory function is reached in most cases after stone removal (Makdissi et al. 2004, Su et al. 2009), and about half the submandibular glands showed a normal histological pattern after sialolith removal (Marchal et al. 2001b).

Gland-preserving treatment options include transoral stone removal techniques, interventional sialendoscopy, extracorporeal shockwave lithotripsy (ESWL), or a combination of these techniques (Iro et al. 2009). Submandibular stones that can be palpated up to the hilar region can be removed transorally by using various techniques. Zenk et al. (2001) have described an expanded duct excision from the papilla to the stone with hilar marsupialization, whereas McGurk et al. (2004) and Capaccio et al. (2011) prefer to perform an oblique incision to the mucosa from the papilla along the floor of mouth, bluntly dissect the duct, release and preserve the lingual nerve, and make a limited duct incision directly over the palpated stone. Also, a limited incision directly over the stone and blunt dissection have been used (Shashinder et al. 2011). Success rates of transoral submandibular stone removal vary from 79–98% (Roh & Park 2008, Combes et al. 2009, Iro et al. 2009, Zhang et al. 2010, Capaccio et al. 2011, Park et al. 2012, Zenk et al. 2012, Schapher et al. 2017). However, approximately 15% of residual concrements or recurrence of obstructive symptoms following surgery of Wharton's duct via the transoral route have been observed in some studies (Zhang et al. 2010, Gerni et al. 2017).

The role of duct marsupialization after transoral sialolith removal is controversial, but in a prospective, randomized, controlled study, Roh and Park (2008) found that sialodochoplasty had no effect on preventing symptom recurrence. Similar findings were observed in a cross-sectional study of 150 patients treated with transoral sialolithectomy with or without sialodochoplasty. Sialodochoplasty did not affect the rate of symptom recurrence but did increase postoperative hypoesthesia, need for general anesthesia (GA), and operating time (Park et al. 2012).

ESWL is a non-invasive method introduced in the early 1990s to fragment salivary stones. The shockwaves may be generated extracorporeally using piezoelectric or electromagnetic techniques and carried out with ultrasound

guidance. A large multicenter study of 2 102 cases reported complete success rates after ESWL treatment for parotid stones in 70% and submandibular stones in 41% of cases. The technique was partially successful in a further 26% of cases (Iro et al. 2009). The efficiency of ESWL can be enhanced by compounding it with sialendoscopy (Zenk et al. 2012). However, the rate of success for sialolithotripsy clearly decreases with the increase in stone diameter (Escudier et al. 2010).

Sialendoscopy has improved the treatment options of sialolithiasis, and this technique is introduced later in the sialendoscopy paragraph.

Submandibulectomy remains as the last treatment option for patients with persistent symptoms after mini-invasive treatment attempts. Studies have shown that the need for submandibular excision has decreased significantly after the development of sialendoscopy and nowadays is under 5% (Kopec et al. 2013). Parotidectomy is rarely performed today because of sialoliths due to its invasive nature, risk of complications, and the success achieved with more conservative approaches.

2.4 Chronic sialadenitis

Chronic sialadenitis most often affects the parotid glands and is characterized by repeated episodes of swelling and tenderness of the affected gland, which might slowly progress into more frequent and persistent symptoms with time (Watkin & Hobsley 1986). The exact pathogenesis of chronic sialadenitis is not completely understood, but it is likely to be multifactorial. The primary pathophysiological event is thought to be decreased salivary production or obstructive stagnation. As a result, there is insufficient salivary flow, which can lead to ascending salivary duct infection via the oral cavity and progress to acute bacterial infection or frequent opportunistic infections (Travis & Hecht 1977, Motamed et al. 2003, Butt 2012). According to Harrison et al. (1997), the microsialoliths, also found in normal salivary glands, can be important in the pathophysiology of chronic sialadenitis, impacting the small intraglandular ducts and causing obstructive atrophy where the ascendant microbes can proliferate and cause further inflammation. Recurrent inflammatory reactions lead to strictures, sialectasis, ductal ectasia, fibrosis, and acinar atrophy accompanied by a lymphocytic infiltration. Thus, a further reduction of salivary flow follows (Travis & Hecht 1977, Seifert 1997, Bhatty et al. 1998). Many local factors causing retardation and obstruction of the duct, including sialoliths, strictures, kinks, and plaques, have been associated with chronic sialadenitis (Zou et al. 1992, Yu et al. 2008, Vashishta & Gillespie 2013). However, it is often unclear whether the disease is the result of primary obstruction with secondary infection and inflammation or primary infection and/or inflammation with secondary obstruction.

Autoimmune diseases are responsible for a small number of chronic sialadenitis. Sjögren's syndrome (SS) is the most ruling, but some other immune-mediated diseases, such as immunoglobulin G4-related disease (IgG4-RD), sarcoidosis (Vourexakis et al. 2010, Ungprasert et al. 2016), granulomatosis with polyangiitis (Barrett 2012), and systemic lupus erythematosus (Shacham et al. 2011), are encountered in the salivary glands. Radiation and radioiodine treatment may also induce inflammation and progressive damage with strictures and fibrosis, leading to chronic obstructive sialadenitis and hyposalivation (Mandel & Mandel 2003, Wu et al. 2015a, Hong et al. 2017). Baer et al. (2017) stated that there might be an allergic etiology in some cases of recurrent salivary gland swelling with eosinophil-rich mucus plugs or sialodochitis with periductal eosinophilic infiltration. Sometimes the recurrent parotitis of childhood can persist into adulthood (Shacham et al. 2009, Wang et al. 2009). The treatment of chronic sialadenitis should be targeted against the etiological factor, if identified, and the revealing of symptoms. In many cases, however, the etiology remains unclear.

2.4.1 Chronic recurrent parotitis

Chronic recurrent parotitis, also called idiopathic or non-specific parotitis, commonly designates chronic salivary gland inflammation without a definable cause. It is characterized by intermittent, mildly tender, uni- or bilateral swelling of the parotid gland, which might persist from days to weeks or even months (Nahlieli et al. 2004a). There is a female predominance, and the age distribution is typically 40–60 years (Seifert 1997). The etiology remains unclear, but a marked reduction of salivary flow usually occurs, and the secretion is viscous and milky (Baurmash 2004). There is an electrolyte concentration change in the acute stage in the parotid fluid, especially in levels of sodium and chloride, but the relevance of this finding remains controversial (Mandel & Baurmash 1980, Baurmash 2004). Also, elevated levels of some serum proteins, such as albumin and lactoferrin, have been measured in the acute phase. Baurmash (2004) has suggested that serum proteins leak into the salivary ducts and coagulate as a consequence of gland inflammation, thus causing obstruction, further inflammation, and damage. Repeated episodes of acute infections may lead to mucus metaplasia of the ductal epithelium, resulting in increased mucous content of secretion, stasis, and further inflammation (Bhatty et al. 1998). Sialography usually demonstrates ductal sausaging with strictures and dilations as well as punctate sialectasia and acinar atrophy (Wang et al. 1992).

2.4.2 Juvenile recurrent parotitis

Juvenile recurrent parotitis (JRP) is a nonspecific recurrent parotid gland inflammation in children, and in the current era, it is the most common cause of parotitis in children in Western countries. The etiopathology of JRP is unclear, although immunodeficiency with hypogammaglobulinemia, isolated immunoglobulin deficiency (Marsman & Sukhai 1999, Fazekas et al. 2005), autoimmune diseases, an early stage of SS (Cimaz et al. 2003, Baszis et al. 2012), congenital parotid malformations, infections, microbes (Ericson et al. 1991, Giglio et al. 1997), and genetics (Reid et al. 1998, Kolho et al. 2005) have been proposed. According to an epidemiological questionnaire of over 700 Finnish adolescents, the rate of verified episode(s) of JRP was 1.1% (Saarinen et al. 2013). The peak onset of symptoms is from four to six years (Kolho et al. 2005), and the symptoms usually resolve after puberty. The recurrent uni- or bilateral swelling and pain of the parotid gland, and sometimes fever, are the main symptoms, even though the overall condition remains good (Saarinen et al. 2013). A male predominance has been described, although females are affected more after puberty (Kolho et al. 2005, Wang et al. 2009).

Characteristic endoscopic findings of JRP include pale, atrophic ductal mucosa and intraductal debris, and there are also sometimes strictures, stenosis, and kinks (Shacham et al. 2009). Diffuse microcalcification throughout the parotid glands can often be seen in radiographic imaging. Even in patients with unilateral symptoms, bilateral gland disease on imaging is often demonstrated (Rosbe et al. 2015). Since JRP usually resolves in puberty, symptomatic treatment with NSAIDs, milking, sialogues, and watchful waiting have replaced the other invasive treatment methods. The role of antibiotics remains controversial. In 2004, Nahlieli et al. (2014b) first reported the results of the endoscopic treatment of JRP, and sialendoscopy has nowadays been used as a treatment option for JRP.

2.4.3 Sjögren's syndrome

SS is a systemic autoimmune disease characterized by lymphocytic infiltration and chronic inflammation of the exocrine glands, mainly the lacrimal and salivary glands, and is often accompanied by extraglandular manifestations (Fox 2005). SS has a strong female propensity, and the age of onset is usually from four to six decades. Most individuals present with xerophthalmia and xerostomia, and about one-third have chronic salivary gland swelling (Baldini et al. 2014). The parotid gland is the most frequently affected, and the bilateral manifestation is not rare. The most common findings in sialendoscopy are a pale, avascular ductal wall, mucus plugs, and strictures (Shacham et al. 2011, De Luca et al. 2015, Jager et al. 2016). Patients have an increased risk of lymphoma, and in case of persistent

salivary gland swelling, ultrasound (US) or magnetic resonance imaging (MRI) with fine needle biopsy should be considered (Zenone 2012). Usually, dry mouth and eyes are treated with local hydrating and lubricating substances. Recurrent swelling of the salivary glands is treated with NSAIDs and short-term glucocorticoid therapy in selected cases. Systemic glucocorticoids and immunosuppressant medicines are used to treat extraglandular manifestations (Saraux et al. 2016).

2.4.4 Chronic sclerosing sialadenitis

Chronic sclerosing sialadenitis (CSS) is a chronic inflammatory disorder that causes salivary gland enlargement. CSS was initially described by Kuttner in 1896 with the presence of firm, painless, and persistent salivary gland swelling commonly affecting the submandibular gland(s) (Geyer et al. 2010). Bilateral, painless parotid, submandibular, and lacrimal gland enlargement was historically termed as Mikulicz's disease. In the recent definition, Kuttner's tumor and Mikulicz's disease are now classified as subcategories of IgG4-related sialadenitis, which belong to the larger group of IgG4-RD (Yamamoto et al. 2006, Geyer et al. 2010). However, not all CSS is related to IgG4. Especially in the Finnish population, the rate of IgG4-related sialadenitis is low (Peuraharju et al., unpublished data). IgG4-related sialadenitis presents in middle-aged or older patients and has an equal gender distribution (Mulholland et al. 2015, Hong et al. 2017). Orbital manifestations and cervical lymphadenopathy are frequent coexisting conditions in the head and neck region, but almost any organ can be involved (Mulholland et al. 2015). It is important to discriminate IgG4-related sialadenitis from other diseases such as lymphoma, epithelial malignancies, and other inflammatory processes since a good response to steroid treatment has been described (Yamamoto et al. 2006, Mulholland et al. 2015).

2.4.5 Treatment of chronic sialadenitis

The treatment of chronic sialadenitis consists of revealing the symptoms and preventing recurrences. The conservative treatments with sialagogues, hydration, gland massage, mouth rinses, and NSAIDs are used to stimulate saliva secretion and to maintain good oral hygiene in order to reduce the risk of ascending infections. Antibiotics should be used in case of acute infection (Zou et al. 1992, Motamed et al. 2003). This might be sufficient, especially in mild cases, and some patients have a spontaneous improvement of symptoms with symptomatic treatment alone (Watkin & Hobsley 1986).

Different medicines like hyaluronidase, iodized oil, antibiotics, and steroids have been injected intraductally to treat chronic sialadenitis. Injecting sclerosing

agents such as methyl violet or tetracycline into the parotid duct has been reported to induce widespread fibrosis, atrophy, and glandular destruction with a resolution of symptoms (Zou et al. 1992, Bowling et al. 1994, Wang et al. 1998). Good results have been described with an intraductal installation of penicillin, but equally good results were reached in a control group with saline instillation, indicating that irrigation itself might be the most important factor, not the antimicrobial effect of the penicillin (Antoniades et al. 2004). It has been suggested that lavage removes mucus plugs and other inflammatory products, eliminating the local source of infection, and dilates the duct, breaking the vicious cycle of decreased secretion, stasis, and inflammation (Baurmash 2004).

Few studies and case reports have described the use of botulinum toxin injections in the treatment of chronic sialadenitis (Ellies et al. 2004, Capaccio et al. 2008), Stensen's duct stenosis (Kruegel et al. 2010, Trapeau et al. 2017), and SS (Daniel & Diamond 2011, O'Neil et al. 2016) with good results. A botulinum toxin injection reduces the secretory capacity of the gland and alleviates the obstructive symptoms. However, repeated injections at regular intervals are needed as the symptoms usually recur (Lovato et al. 2017).

Parotid duct ligation has been described as a treatment method of chronic parotitis. This is thought to induce pressure atrophy and necrosis of the acini, leading to symptom improvement. However, the studies include only a limited number of patients, and the results have been controversial, with high a failure rate of 50% or more (Nichols 1977, Motamed et al. 2003, Baurmash 2004).

In tympanic neurectomy, the parasympathetic nerve supply to the parotid gland is interrupted by dissecting the parasympathetic fibers at the tympanic plexus via a tympanic approach. This is theorized to result in atrophy of the parotid gland by reducing the stimulus for salivary production and secretion (Mandour et al. 1977). In a retrospective study of 49 patients with chronic parotitis treated by tympanic neurectomy, a total or partial resolution of symptoms was reported in 82% of patients (Vasama 2000). However, the chorda tympani nerve carries some parasympathetic fibers to the parotid glands as well, which might explain the variable results (Perera et al. 2000).

Sialendoscopy has proven to be a promising treatment option for chronic sialadenitis, with the possibility to dilate strictures, flush the mucus plugs, and administer medicines intraductally. This technique is discussed in more detail later.

Sialadenectomy is an efficient treatment method for chronic sialadenitis but, in relation to complications, it should be considered only when other less invasive procedures fail. Controversy still exists as to the extent of the parenchymal resection required in parotidectomy and whether to ligate the duct (Nouraei et al. 2007, Patel et al. 2007, Sharma 2013).

2.5 Noninflammatory diseases of the salivary glands

Benign noninflammatory diseases of salivary glands include, e.g., salivary gland tumors, cysts, sialadenosis, and radiation or radioiodine (RAI)-induced sialadenitis. Sialendoscopy, so far, has no indication in the treatment of tumors, cysts, or sialadenosis, but sialadenosis might occasionally be confused with chronic sialadenitis. Little experience exists in the treatment of RAI-induced sialadenitis with sialendoscopy with promising results (Cung et al. 2017).

2.5.1 Sialadenosis

Sialadenosis, also known as sialosis, is an asymptomatic non-inflammatory condition characterized by the bilateral enlargement of the salivary glands, most commonly involving the parotid glands. It has a multifactorial etiology and is most commonly related to alcoholism, diabetes mellitus, endocrinopathy, chronic liver disease, bulimia, hyperlipidemia, obesity, or malnutrition. Also, the use of certain medicines, mainly antihypertensives or anticholinergic drugs, may induce sialadenosis (Scully et al. 2008, Guggenheimer et al. 2009). Peripheral autonomic neuropathy is thought to be the unifying feature. The diagnosis is based on the patient's history, US, or MRI to exclude other pathologies, and biopsy in unclear cases (Scully et al. 2008).

2.5.2 Radioiodine-induced sialadenitis

RAI therapy has been commonly used after total thyroidectomy for patients with papillary and follicular thyroid cancer. One of the most frequent complications of RAI therapy is salivary gland dysfunction with recurrent swelling and pain in the affected glands, and xerostomia (Lee et al. 2015, Moreddu et al. 2017). The salivary injury is related to the ability of the salivary glands to concentrate ^{131}I. Serous acini have shown increased uptake of ^{131}I compared to mucinous acini, resulting in an over-representation of parotid gland involvement (Mandel & Mandel 2003). RAI-induced sialadenitis can have a significant reduction on patients' quality of life (QoL) (Dingle et al. 2013), and the conservative treatment with NSAIDs, hydration, gland massage, sialogues, and steroids is not sufficient for a significant portion of patients. Treatment of RAI-induced sialadenitis with sialendoscopy is discussed later in more detail.

2.6 Radiological imaging of the salivary glands

Different imaging modalities are used in the diagnosis of salivary gland diseases. The US is a cheap, noninvasive, and tolerable but operator-dependent method widely used as the first imaging tool. It can detect tumors, local and diffuse lesions, dilated ducts, intraglandular microcalcification, and stones (Abdel Razek & Mukherji 2017).

Studies comprising the US as a diagnostic tool for sialolithiasis have demonstrated sensitivity and specificity between 65–95% and 80–95%, respectively (Terraz et al. 2013, Patel et al. 2014, Schwarz et al. 2015b, Thomas et al. 2017, Goncalves et al. 2018). False-negative findings are usually associated with calculi with a diameter of less than three millimeters, soft consistency, and located in the distal duct. False-positive findings are mainly caused by ductal stenosis, scars, and extraductal calcification (Terraz et al. 2013, Goncalves et al. 2018). Larson et al. (2017) reported in a prospective study that surgeon-performed US is an accurate way to confirm or rule out sialolithiasis as well as to diagnose but not necessarily rule out salivary duct stenosis and estimate outcomes. Oral application of ascorbic acid seems to improve visualization of the salivary duct in cases of obstruction (Bozzato et al. 2009).

Other imaging modalities to detect salivary gland pathologies are sialography, standard computed tomography (CT), or cone beam computed tomography (CBCT), MRI, and magnetic resonance (MR) sialography. Because of the excellent delineation of the ductal system, sialography has been considered the gold standard for assessing ductal pathology, but related to new imaging techniques and the limitations of sialography, such as ionizing radiation, the need for contrast media, and pain and invasiveness related to the procedure, its role has decreased (Zenk et al. 2009).

CT or CBCT are particularly useful if there is suspicion of a sialolith with a sensitivity of approximately 80–98% and a specificity of 90%, but the patient is exposed to the radiation (Schwarz et al. 2015, Thomas et al. 2017). MR sialography has shown to be an excellent technique for visualizing the ductal system up to the tertiary branches and the parenchymal tissue detecting sialoliths, strictures, and stenosis, as well as changes related to chronic sialadenitis (Kalinowski et al. 2002, Ren et al. 2015). It is non-invasive, safe, and does not require a contrast medium, but it is dependent on salivary flow.

The scintigraphy technique uses Technetium-99m-pertechnetate and is applied as an objective technique to assess salivary gland function as it measures the degree of radioisotope uptake and excretion, but due to its rarity and expenses, it is used mostly in research and has less relevance in the clinical routine (Makdissi et al. 2004, Su et al. 2009).

2.7 Sialendoscopy

Sialendoscopy was developed in Europe to meet the demand for a less invasive method to treat salivary obstruction. Sialendoscopy allows the endoscopic exploration of the salivary ducts up to the level of secondary and even tertiary branches and offers an opportunity to treat salivary duct obstruction (Marchal et al. 2000, Nahlieli & Baruchin 2000). The studies that have evaluated the diagnostic and therapeutic outcomes of sialendoscopy indicate that it is effective and safe in the treatment of obstructive sialadenitis (Marchal et al. 2002, Nahlieli & Baruchin 2000, Koch et al. 2012a), and it seems to be efficacious in the treatment of inflammatory sialadenitis and sialodochitis as well (Vashishta & Gillespie 2013, Ramakrishna et al. 2015). Due to the spread of sialendoscopy, there is less need for sialadenectomies. In a nationwide review of data from Denmark, there was a 26% reduction of gland excisions performed because of benign salivary gland disorders after the introduction of sialendoscopy when compared to the 5 years priory (Rasmussen et al. 2016). The only relative contraindications for sialendoscopy are complete distal obliteration of the duct and the restricted opening of the mouth, as the introduction of the endoscope may not be possible, and acute suppurative sialadenitis, as visibility might be poor, and there is an increased risk for ductal perforation (Nahlieli et al. 2006a).

2.7.1 History of sialendoscopy

The first reported attempts to visualize the salivary duct were performed in the early 1990s. Koningsberger et al. (1990) and Gundlach et al. (1990) used a flexible endoscope combined with intracorporeal laser lithotripsy for the fragmentation of calculi in the salivary glands. In 1991, Katz (1991) introduced a flexible mini-endoscope with the intent to diagnose diseases of the ductal system of the major salivary glands and to remove salivary stones with a Dormia basket in a blind technique. In 1994, Arzoz et al. (1996) used a rigid 2.1 mm mini-ureteroscope with a working channel of 1 mm and an intracorporeal pneumoballistic lithotriptor or laser to fragment and remove the calculi. In the same year, Nahlieli et al. (1994) described the use of a rigid mini-arthroscope to diagnose and treat salivary gland obstruction, and in 1997, Nahlieli and Baruchin published their three-year experience of this new technique. During 1994–1999, Nahlieli and Baruchin (2000) treated 236 patients with endoscopy with a success rate of 83% and introduced a semi-rigid sialendoscope specially developed for the salivary glands. In 2000, Marchal et al. (2000) reported a similar experience and results with sialendoscopic techniques. In 2007, Marchal described the combined endoscopic-external method for the removal of major salivary stones.

During the 1990s and 2000s, major advances in optical technologies and the development of semi-rigid high-quality endoscopes that are small in diameter have established the role of sialendoscopy in a reliable and safe technique for the diagnosis and treatment of salivary gland disorders in adults and children (Marchal et al. 2002, Nahlieli et al. 2004b, Zenk et al. 2004).

Figure 2 All-in-one sialendoscope and instruments used during sialendoscopy: a knife, conic dilators, tweezers, salivary probes, scissors, and criles. Photograph: Antti Mäkitie.

2.7.2 Diagnostic sialendoscopy

In most cases, diagnostic sialendoscopy can be performed under LA after dilation of the papilla. The procedure can be performed either in a sitting or supine position. The sialendoscope and the main instruments used during sialendoscopy are photographed in Figure 2. Sometimes, mini-papillotomy is necessary to introduce the endoscope into a duct (Marchal et al. 2002, Nahlieli et al. 2003). While navigating in the duct, intermittent rinsing through the endoscope is used to dilate the duct, ensure the visualization, and remove debris. Isotonic saline with local anesthetic solution has often been used for this purpose (Marchal et al.

2002, Nahlieli et al. 2003). The success rates for diagnostic sialendoscopy have varied from 75–100%, usually being around 95–98% with more failures related to cases with SS (Chuangqi et al. 2013, Pace et al. 2014, Gallo et al. 2016, Karagozoglu et al. 2017).

Sialendoscopy has proven highly efficient in detecting any ductal changes. With sialendoscopy, stenosis and strictures, for example, can be precisely assessed with regard to their location, extent, degree of the luminal diameter, number, and tissue quality (Koch & Iro 2017), and sialoliths are evaluated by their exact location, size, mobility, and adhesion to the ductal wall (Luers et al. 2011). Chuangqi et al. (2013) performed sialendoscopy for 561 patients with obstructive symptoms and evaluated the pathological features and changes, which were noted in 98% of sialendoscopies. Many microanatomical and pathophysiological features of the ductal lumen have been noticed with the help of sialendoscopy, such as changes in the ductal wall after long-standing inflammation with a matted appearance, ecchymosis and paucity of blood vessels, ductal polyps, intraparenchymal sialoliths located close to the ductal system, a pelvis-like formation in the submandibular hilum and sphincter-like mechanisms in Wharton's duct near the papilla and in Stensen's ducts more posteriorly (Nahlieli & Baruchin 2000, Chuangqi et al. 2013). The sialendoscopic views from the normal parotid duct, floating sialolith, and chronic inflammation are presented in Figure 3.

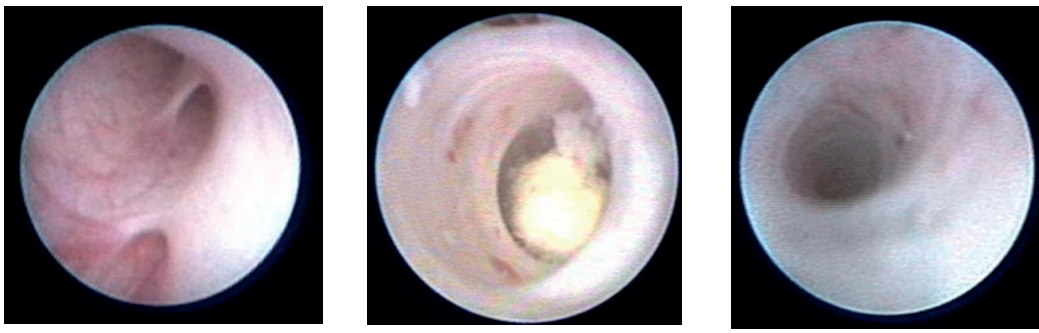

Figure 3 Sialendoscopy views of a normal parotid duct, floating sialolith inside the submandibular duct, and an avascular ductal wall of the chronic parotitis patient. Photographs: Riitta Saarinen.

2.7.3 Interventional sialendoscopy

2.7.3.1 Treatment of sialoliths

Endoscopic sialolith removal

The prognostic factors predicting successful outcomes in sialendoscopic stone removal are small size, good mobility, round or oval shape, distal location, and shorter duration of symptoms (Luers et al. 2011, Luers et al. 2012a). Stones not larger than 4–5 mm can be retrieved using baskets, microdrills, graspers, or micro forceps with a success rate of over 80% (Nahlieli et al. 2003, Nahlieli et al. 2006a, Walvekar et al. 2009, Zenk et al. 2012), while Luers et al. (2011) observed that the success rate drops to 20% in stones exceeding 5 mm, and Marchal et al. (2001a) noticed that only 35% of sialoliths larger than 3 mm were able to be removed endoscopically without fragmentation. In a study of 942 sialolithiasis patients treated with several different methods, Zenk et al. (2012) observed that the longest mean diameter of a sialolith that can be removed by sialendoscopy alone is 4.2 mm in the parotid and 4.9 mm in the submandibular gland, confirming the size limit of 3–5 mm given in the algorithms for successful endoscopic stone removal (Marchal & Dulguerov 2003, Koch et al. 2009). However, mobility of the stone seems to be the most important factor in predicting success in endoscopic sialolith removal. In a study of 49 sialolith patients, the mobile stones were able to be removed endoscopically in 92% of the cases (Luers et al. 2011). Iro et al. (2009) reported a successful basket or mirco forceps retrieval rate of 92% among the 1522 patients with mobile sialoliths under 5 mm in diameter.

In the majority of cases, prior fragmentation or transductal surgery is necessary due to the sialolith's size and adherence (Zenk et al. 2012). Various methods of intraductal fragmentation have been developed for stones that are achievable endoscopically, including mechanical fragmentation, using a micro drill or micro forceps (Nahlieli et al. 2003), lasers (Durbec et al. 2012, Phillips & Withrow 2014), and electrohydraulic (Marchal et al. 2002, Nakayama et al. 2007) or pneumatic lithotripsy (Koch et al. 2019). Recent results with intraductal laser lithotripsy have success rates of over 80–90%, and the holmium laser has been the most frequently used (Durbec et al. 2012, Phillips & Withrow 2014, Sionis et al. 2014). However, the laser should be used only in clear vision, and the surgeon should be aware of potential dangers such as absorption in the surrounding tissue and heat generated from the fragmentation since complications have been described after laser fragmentation in the form of serious trauma with total obliteration of the duct and ductal perforation (Durbec et al. 2012, Sahin-Yilmaz & Oysu 2015). The preliminary experiences of intraductal pneumatic lithotripsy have been promising, with success rates of 88–98% (Serbetci et al. 2017, Koch et

al. 2019). Koch et al. (2019) performed a checkup endoscopy on the first and second days to remove residual fragments and fibrinous plaques, and at the 4- and 8-week checkups, they found no severe scar formation or stenosis.

Figure 4 Basket removal of the sialolith from the submandibular duct. Photograph: Riitta Saarinen.

Sialendoscopy-assisted transoral removal of submandibular sialoliths

Sialendoscopy-assisted transoral stone removal is possible in patients with submandibular sialoliths situated in the main duct or hilar region with high success rates of 87–95% (Iro et al. 2009, Su et al. 2010, Zenk et al. 2012, Liu et al. 2013). In this technique, the sialolith is verified with a sialendoscope, and afterward, an incision is made in the mucosa. The floor of the mouth is then raised with digital pressure from the submandibular region, and a limited incision is made in the duct over the stone with the help of the endoscope light (Marchal 2007, Su et al. 2010, Liu et al. 2013). Prophylactic antibiotics are often used (Liu et al. 2013, Schwartz et al. 2015a), and many authors favor the use of stents left in place for varying times (Marchal 2007, Su et al. 2010, Liu et al. 2013, Schwartz et al. 2015a). This approach is particularly valuable in immobile, non-palpable stones (Fabie et al. 2019). Other advantages are the possibility of identifying or ensuring the exact location of the stone and exploring the remaining duct against residual stones or strictures.

Sialendoscopy-assisted transoral removal of parotid sialoliths

Sialendoscopy-assisted transoral stone removal has been used for impacted parotid stones located distally. In this technique, a semicircular mucosal incision is made approximately 1 cm anterior to the papilla, and after submucosal dissection, the duct is exposed and incised longitudinally over the stone. A

sialendoscopic control of the whole duct tree is then performed and the duct is closed with stitches. Stents are often used to prevent scarring (Overton et al. 2012, Zheng et al. 2015, Foletti et al. 2016, Ye et al. 2017). In a retrospective study of 22 patients with parotid sialoliths, Foletti et al. (2016) concluded that this technique is recommendable for the anterior-third parotid duct sialoliths located in front of the anterior edge of the masseter with a success rate of 88%, but there are limitations for more posterior stones with success rates of 63% and 25% in the removal of the middle-third and posterior-third sialoliths, respectively.

Sialendoscopy-assisted transcutaneous removal of parotid sialoliths

Sialendoscopy-assisted transcutaneous removal of parotid stones is used if endoscopic removal is not possible due to large size, adherence, or intraglandular location of the stone. The sialendoscope is used to localize the stone, and the stone is removed externally using a modified Blair incision (Carroll et al. 2013, Ong et al. 2017), a modified facelift incision (Marchal 2007, Capaccio et al. 2014), or an incision directly over the stone (Nahlieli et al. 2002, Rotnagl et al. 2016). Facial nerve monitoring is recommended (Koch et al. 2013, Kopec et al. 2013a, Konstantinidis et al. 2015, Ong et al. 2017). When the sialolith has been removed, the duct is visualized for further stones, after which it is repaired and the parotid fascia is closed. Many studies describe the use of stents for the reconstruction of Stensen's duct (Nahlieli et al. 2002, Koch et al. 2013, Klein & Ardekian 2014, Konstantinidis et al. 2015, Rotnagl et al. 2016). Prophylactic antibiotics are used often (Nahlieli et al. 2002, Karavidas et al. 2010, Ong et al. 2017), and a few studies report the administration of perioperative steroids to prevent swelling and decrease the risk of ductal stenosis (Carroll et al. 2013, Rotnagl et al. 2016, Ong et al. 2017). The review of published articles on the focus of sialendoscopy-assisted transcutaneus removal of parotid sialoliths in Table 1 shows success rates between 75–100% for this technique. The high-resolution US has also been used to identify the exact location of the sialolith alone or in combination with the endoscope and is especially useful in cases where navigation with the endoscope is impossible (Nahlieli et al. 2002, Karavidas et al. 2010, Carroll et al. 2013).

Table 1. Sialendoscopy-assisted transcutaneous removal of parotid sialoliths

Author, year	Data collection	Sample size	Mean stone size, mm (range)	Incision technique	Anesthesia	Mean/median follow-up, mo (range)	Successful stone removal	Resolution of symptoms	Complications (number)
Capaccio et al. 2014	2009–2013	8	12.6 (2–20)	Preauricular incision (n=6), limited incision (n=2)	GA/LAS	19 (6–45)	88%	88%	None
Carroll et al. 2013	2010–2012	14	8.7 (2–12)	Modified Blair incision	GA	12 (9–26)	93%	71%	Preauricular anesthesia (2), sialocele (1), fistula (1)
Karavidas et al. 2010	1999–2007	69	7.2 (3–15)	Preauricular incision (n=47), limited incision (n=22)	GA/LA	25 (2–81)	99%	97%	Duct perforation (1), macerated duct (1), acute parotitis (2), stricture (1), visible scar (1)
Klein et al. 2014	2011–2012	6	8	Facelift approach	GA	(4–23)	100%	100%	None
Koch et al. 2013	2006–2012	17	9.2 (4–16)	Preauricular incision	GA	41 (3–68)	94%	94%	Hematoma (1)
Konstantinidis et al. 2015	2011–2014	12	8.1 (2–12)	Preauricular incision	GA	15.5 (13–20)	100%	100%	Hematoma (1), stent extrusion (1), acute parotitis (1)
Kopec et al. 2013	2008–2011	5	NR	Preauricular incision (n=3), limited incision (n=2)	GA	20 (2–29)	100%	100%	None
Marchal 2007	NR	37	NR	Facelift approach	GA	19	100%	92%	None
Mikolajczak et al. 2015	2008–2013	10	8.7 (7–12)	Preauricular incision (n=5), limited incision (n=5)	GA	15 (6–39)	100%	100%	Sialocele (2)
Numminen et al. 2014	2009–2012	8	7.6 (7–10)	Preauricular incision (n=7), limited incision (n=1)	GA	21.5 (2–43)	75%	75%	None
Rotnagl et al. 2016	2009–2016	9	6.8	Limited incision	GA/LA	(12–36)	100%	89%	External secretion of saliva from the wound (2)
Ong et al. 2017	2010–2015	44	8.4 (2–20)	Modified Blair incision	GA	11	98%	87%*	Preauricular anesthesia (4), fistula (2), sialocele (2), suture granuloma (1), persistent wound drainage (1)

*follow-up information available 38/44; 55% complete resolution, 32% partial resolution
NR, not reported

2.7.3.2 Treatment of strictures and stenosis

Classification of stenosis

Koch & Iro (2017) analyzed the sialendoscopy findings of 550 symptomatic stenoses of Stensen's duct and classified each in relation to tissue characteristics and appearance: type 1 stenosis (8.9%) was characterized by inflammatory changes, type 2 (19.5%) was associated with circular or weblike changes and ductal dilatation, and type 3 (71.6%) was characterized by fibrotic reactions with diffuse involvement of the duct. They also used a sialendoscope to grade the narrowest part of the stenosis from I (passable with 1.1 mm endoscope) to IV (complete stenosis) (Koch & Iro 2017). Stenosis can also be classified based on its location. Most stenoses are found in the middle or distal regions of the duct, while only 8–18% of Stensen's duct stenoses and approximately 18% of Wharton's duct stenoses are located in the proximal segment (Koch et al. 2009, Koch et al. 2012b, Kopec et al. 2013b, Koch & Iro 2017).

Sialendoscopy-assisted treatment of duct stenosis

The location, grade, and tissue characteristics are the most important factors when treating duct stenosis. In a series of 153 symptomatic stenoses of the submandibular duct, transoral surgery with papillotomy or extended ductal incision and marsupialization were used in 58% of cases, most often in distal stenosis. Endoscopic treatment with dilatation of the stricture with a basket or micro drill were used for 27% and cortisone irrigation alone in 12%. Repeated intraductal cortisone instillation was carried out for endoscopically treated patients after the procedure (Koch et al. 2012b). Kopec et al. (2013b) used a micro-instrument, such as the micro burr, and Nahlieli et al. (2001) mainly used balloons to dilate the strictures of Wharton's and Stensen's ducts. Ardekian et al. (2010) treated 87 parotid duct stenoses with hydrostatic pressure and the sialendoscope itself or more advanced cases with sialo-balloons or forced manipulation with microdrills. Stents have been actively used, and a significant improvement of symptoms has occurred in approximately 80% of cases (Nahlieli et al. 2001, Ardekian et al. 2010, Kopec et al. 2013b).

Koch et al. (2012a) presented a study of 93 patients with 111 stenoses in Stensen's duct. Endoscopic dilatation of stenosis with a basket or micro drill was used successfully in 59% of cases, hydrostatic pressure and cortisone irrigation as the only treatment in 22%, and transductal surgery with papillotomy, distal ductal incision, or ductal resection with reinsertion and stent placement in 8.6%. Steroids seemed beneficial in cases of inflammatory stenosis with ductal edema and hyperemia. The gland preservation rate was 96%. In 2014, Koch et al. (2014) published long-term follow-up results from 82 out of 93 patients with Stensen's

duct stenosis who were treated during 2001–2006, as described previously. After an average follow-up of 98 months, 50% of patients were symptom-free, while 50% of patients continued to have low-grade swelling and 20% continued to have pain.

The sialendoscopy-assisted transcutaneous treatment of difficult Stensen's duct stenosis with vein patch or replacement of the duct by vein interposition has also been described (Koch et al. 2013).

2.7.3.3 Treatment of chronic sialadenitis

During the past decade, promising results have been reported in the treatment of chronic sialadenitis, including JRP, chronic recurrent parotitis, autoimmune-related sialadenitis, and RAI-induced sialadenitis (Nahlieli et al. 2004a, Shacham et al. 2009, Shacham et al. 2011, De Luca et al. 2014, Bhayani et al. 2015, Delagnes et al. 2017a, Jager et al. 2016, Capaccio et al. 2017). The therapeutic options for sialendoscopy are the irrigation and removal of mucus plugs and debris, dilatation of stenosis and strictures, and infusion of medicines to reduce the inflammation. Intraductal steroids have often been used in a lavage solution or as a dosage after sialendoscopy, but other drugs such as iodized oil, antibiotics, and chymotrypsin have also been tried therapeutically (Yu et al. 2008, Vashishta 2013, Sun et al. 2017). Delagnes et al. (2017a) observed that concurrent use of triamcinolone irrigation with sialendoscopy is associated with better symptom resolution in patients with non-sialolith sialadenitis, but in multivariate analysis, this finding was not statistically significant. Capaccio et al. (2017) concluded in a prospective, randomized study that a combination of interventional sialendoscopy followed by repeated ductal steroid irrigations at the outpatient clinic produced a better outcome than sialendoscopy alone in the treatment of recurrent sine causa sialadenitis. Recently, Sun et al. (2017) discovered that sialendoscopy with irrigation of chymotrypsin combined with gentamicin was a more effective treatment for chronic non-stone–related obstructive parotitis than sialendoscopy with gentamicin alone.

Treatment of juvenile recurrent parotitis

Many series have reported good results in the treatment of JRP with sialendoscopy, but the population sizes are small and the follow-up periods rather short. In a meta-analysis of 120 patients with JRP, the weighted pooled proportion of success rates for no further episodes after sialendoscopy in patients was 73%. The follow-up times ranged from 0 to 36 months (Ramakrishna et al. 2015). However, despite the potential benefits of sialendoscopy, its role remains controversial in the treatment of JRP. Schneider et al. (2014) compared patients

treated with sialendoscopy with cortisone irrigation to those treated with oral antibiotic therapy alone and found equal therapeutic outcomes. Rosbe et al. (2015) compared the effectiveness and costs of sialendoscopy to conservative therapy and observed similar outcomes with higher costs related to sialendoscopy. Roby et al. (2015) treated JRP patients with intraductal steroid infusion alone and found an improved quality of life in 75% of patients, which is similar to what has been reported after sialendoscopy. A retrospective setup and the absence of randomization and a control group are the limitations in these studies.

Treatment of Sjögren's syndrome–related sialadenitis

Sialendoscopy seems to reduce the symptoms of SS-related sialadenitis. In retrospective studies, an improvement of symptoms has been achieved in 85–100% of patients after a mean follow-up of 6–11 months (Shacham et al. 2011, De Luca et al. 2015). In prospective studies, good results with a reduction of glandular swelling and pain as well as xerostomia have been found after sialendoscopy. Also, marks of increased salivary flow have been noticed (Jager et al. 2016, Capaccio et al. 2017, Karagozoglu et al. 2018). However, it should be considered that improvement in salivary flow is possible only if saliva-producing acinar cells are present, so the stage of the disease is expected to have an important impact on the success (Karagozoglu et al. 2018).

Treatment of radioiodine-induced sialadenitis

Although limited to a small case series, sialendoscopy seems to be effective in the treatment of RAI-induced sialadenitis. Clinical improvement has been observed in 75–100% of patients treated with sialendoscopy (Nahlieli & Nazarian 2006b, Bomeli et al. 2009, Prendes et al. 2012, De Luca et al. 2014). In a prospective study of 26 RAI sialadenitis patients, Bhayani et al. (2015) discovered a complete or partial resolution of symptoms in 92% of patients, while 77% had complete or partial resolution of their xerostomia symptoms. Also, significant improvement in saliva production was seen at the 6-month follow-up. Wu et al. (2015a) found an improved uptake and excretion by salivary gland scintigraphy in 79% of 19 glands. Contrarily, Kim et al. (2016) observed that no significant change was found in xerostomia-related symptoms, salivary flow rates, or scintigraphy functional results in 10 patient series.

Table 2. Indications for sialendoscopy and existing evidence of literature

Disorder	Indication for sialendoscopy	Conservative treatment	Evidence of sialendoscopy	Related studies
Obstructive sialadenitis	Recurrent swelling with tenderness of the affected gland (might be related to eating), detected sialolith, repeated bacterial infections related to mechanical obstruction	Symptoms rarely/ occasionally, random bacterial infections	Good evidence, several studies	Strychowsky et al. 2012 (systematic review and meta-analysis) Atienza & Lopez-Cedrun 2015 (systematic review and meta-analysis)
Sialoliths	All parotid sialoliths, all non-palpable submandibular sialoliths, hilar/intraglandular sialoliths of the submandibular gland	Palpable sialolith in the main duct of the submandibular gland -> transoral removal	Good evidence, several studies	Ryan et al. 2019 (prospective follow-up study) Roland et al. 2017 (systematic review and meta-analysis)
Strictures	Suspicion of stricture/stenosis, obstructive symptoms of unclear origin		Good evidence; several, mainly retrospective studies	Plonowska et al. 2019 (prospective follow-up study) Erkul et al. 2016 (systematic review) Ardekian et al. 2010 (retrospective study) Nahlieli et al. 2001 (retrospective study)
Chronic recurrent parotitis	Repeated or persistent swelling and tenderness of the affected gland, moderate or severe symptoms	Mild or moderate symptoms, symptoms occasionally	Moderate evidence; mainly retrospective case series with submandibular patients also included	Capaccio et al. 2017 (prospective study) Sun et al. 2017 (prospective study) Wu et al. 2015 (retrospective study) Vashishta & Gillespie 2013 (retrospective case series)

JRP	Severe symptoms, diagnostic in unclear cases	Majority of cases with tolerable symptoms	Evidence controversial; small case series, lack of prospective, randomized controlled studies	Garavello et al. 2018 (systematic review) Ramakrishna et al. 2015 (systematic review and meta-analysis) Rosbe et al. 2015 (retrospective observational study) Schneider et al. 2014 (retrospective study)
Sjögren's syndrome	Repeated or persistent swelling and tenderness of the affected gland, moderate or severe symptoms	Mild or moderate symptoms, xerostomia	Moderate evidence; preliminary evidence that sialendoscopy can also improve the symptoms of xerostomia, small sample sizes	Karagozoglu et al. 2018 (prospective, randomized controlled study) Capaccio et al. 2017 (prospective study) Jager et al. 2016 (prospective, randomized controlled study)
RAI-induced sialadenitis	Repeated or persistent swelling and tenderness of the affected gland, moderate or severe symptoms	Mild or moderate symptoms, xerostomia	Moderate evidence; controversial evidence of treatment of xerostomia with sialendoscopy; small case series, lack of prospective, randomized controlled studies	Erkul et al. 2016 (systematic review)

2.7.4 Complications

Diagnostic and interventional sialendoscopy have proven to be safe procedures but not free of complications. Complication rates between 1–30% have been reported depending on the definition, study population, and size (Marchal et al. 2002, Nahlieli et al. 2003, Koch et al. 2005, Nahlieli et al. 2006a, Papadaki et al. 2008, Walvekar et al. 2008, Rasmussen et al. 2012, Gallo et al. 2016, Karagozoglu et al. 2017). The most prevalent complications seem to be ductal perforations (Marchal et al. 2002, Gallo et al. 2016), postoperative strictures (Nahlieli et al. 2006a), and infections (Rasmussen et al. 2012). Temporary lingual nerve paresthesia, wire basket blockages, ranula formation, and hemorrhage have also been described in the literature after interventional procedures (Nahlieli et al. 2006a, Capaccio et al. 2016, Gallo et al. 2016). Complications confronted after endoscopy-assisted transcutaneous sialolith removal are presented in Table 1. Nahlieli (2015) analyzed the complications of 526 patients treated with interventional sialendoscopy due to sialolithiasis. The complications were confronted in 3.2% of cases in the forms of stricture (1.7%), ranula (1.3%), and lingual nerve paresthesia (0.6%). In an Italian multicenter study of 1309 diagnostic and interventional sialendoscopies, the complications were observed in 5.4% of procedures, most often as ductal perforation (Gallo et al. 2016). The main limitation of these studies is their retrospective design, which might underestimate the complication rates.

Postoperative glandular swelling is a normal reaction after sialendoscopy due to ductal irrigation and fluid retention, and it usually resolves after a few hours (Nahlieli et al. 2003). Excessive swelling of the affected gland and submucosal surroundings after sialendoscopy is usually due to perforation of the duct and excessive irrigation. Such swelling usually resolves in approximately 24 hours. However, this complication is important to notice because swelling can, in some cases, cause an airway compromise (Papadaki et al. 2008, Martins-Carvalho et al. 2010). Other major complications that have been described include avulsion of the main duct leading to salvage superficial parotidectomy (Walvekar et al. 2008).

2.7.5 Cost-effectiveness of sialendoscopy

Society often invests in health care without definite knowledge of the health benefit reached. This happens especially when new treatments and technologies are developed. Only a few studies have evaluated the costs and cost-effectiveness of sialendoscopy and sialendoscopy-assisted surgery. Felton et al. (2012) summarized the coding prices of the UK Trust for salivary gland procedures in 2011. The prices for adults were £612 for sialendoscopy ± stone removal, £552 for sialendoscopy ± duct dilatation, and £1962 for submandibular gland excision or

superficial parotidectomy, which shows that sialendoscopy is much cheaper than gland excision. Shashinder et al. (2011) calculated that the average cost of transoral sialolith removal was approximately £197, concluding that this procedure is more cost-effective than other alternative options such as sialendoscopy or gland resection. Rosbe et al. (2015) found that the average costs of care of JRP treated with sialendoscopy ($31,338 per patient) were much higher than those treated conservatively ($698 per patient), but the outcomes were the same. However, this study was not randomized, and the sialendoscopy patients were selected for the operation because their more frequent symptoms making the comparison difficult. Ong et al. (2017) showed that the transfacial sialendoscopy-assisted removal of parotid stones ($22,482) was less expensive and faster compared to the traditional parotidectomy ($30,546) performed because of chronic sialadenitis minimizing the time needed for surgery and maximazing hospital resources, and Kowalczyk et al. (2018) showed that the upfront sialendoscopy is more cost-effective treatment for RAI-induced sialadenitis than medical management utilizing US when the willingness-to-pay threshold is $50,000. Lately, Coniglio et al. (2019) compared the costs of sialendoscopy performed at the office under LA to similar procedures performed in the operating room under GA and noticed a significant reduction in time and financial burden for the patients with the in-office procedure, although the outcomes were similar. However, most of these studies were retrospective. Also, the different build-up of hospital costs in different countries makes comparing the results difficult.

2.8 Assessing health-related quality of life (HRQoL)

No single definition of QoL exists. According to The World Health Organization (WHO), QoL is a broad but complex concept that is affected by a person's physical health, psychological state, personal value and beliefs, social relationships, environment, and level of independence. The WHO defines QoL as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (WHOQOL Group 1994). HRQoL can be used to describe the effects of a disease, disability, or disorder on QoL and the effect of treatment or clinical intervention on health and general well-being. HRQoL is a multidimensional concept that encompasses physical, mental, and social aspects and is affected by the general condition of the individual, other health problems and sicknesses experienced, and the phase of life. HRQoL is a subjective matter, and the individuals themselves should assess it (Guyatt et al. 1993).

The severity and frequency of the disease can be easily measured, but when assessing HRQoL, specific instruments are needed to evaluate the changes over time and under altering living circumstances. Two kinds of HRQoL instruments exist: generic and disease-specific ones. The disease-specific instruments are more sensitive to the effects of a specific disease and intervention in health status, but they are not suited to compare treatment results across various diseases. Generic instruments allow the comparison of diverse patient groups with different underlying disease and clinical interventions to each other and to the general population. They can be classified into profile and single-index score measures. The profile instrument characterizes the health status from the perspective of various physical and emotional dimensions, such as bodily pain, general health, vitality, social and mental functioning, etc. The single-index score instrument is used to produce a single index score, which is needed to calculate the quality-adjusted life-years used to estimate the cost-effectiveness of various interventions (Guyatt et al. 1993). The methods differ among different HRQoL instruments, and when choosing the instrument, one must consider its validity, reliability, sensitivity, and usability (Moock & Kohlmann 2008).

The Finnish 15-dimensional health-related quality of life (15D HRQoL) questionnaire is a standardized and validated, generic, self-administered tool to measure HRQoL. It can be used both as a single index score and as a profile of 15 different dimensions including mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity. A single index score on a scale of 0 to 1 is obtained by incorporating the population-based preference weights to the dimensions, representing the overall HRQoL (Sintonen 2001). The 15D can be used to calculate quality-adjusted life-years, and it has been developed to measure the cost utility of different treatments or interventions in health care (Sintonen 2001). The 15D is shown to be highly reliable and responsive to change, and it compares favorably with other similar instruments (Hawthorne et al. 2001, Moock & Kohlmann 2008).

2.8.1 HRQoL after sialendoscopy

The impact of sialendoscopy on patients' HRQoL has been little explored. No validated disease-specific questionnaire for capturing salivary gland–related QoL exists today, and only a few studies have used validated generic surveys. A study using the Short-Form-36 Health Survey (SF-36) showed significantly worse values in vitality and mental health after sialendoscopy when compared to the age- and gender-matched reference group referring to potentially persisting symptoms. Patients with daily symptoms suffered more bodily pain and felt more

restricted in daily activities than patients with recurrent symptoms. When symptoms were chronic and not ingestion-related, physical functioning decreased (Kroll et al. 2013). The study lacks a preoperative assessment, so the potential benefits of sialendoscopy cannot be estimated. Further, two studies have used the Glasgow Benefit Inventory (GBI) survey to assess the improvement of patients' HRQoL after sialendoscopy. A positive effect was noticed in both studies comparing well with other common otorhinolaryngological procedures where the GBI has been reported (Ianovski et al. 2014, Meier et al. 2015).

The need for a sensitive tool to assess the salivary gland–related symptoms and HRQoL has recently been recognized. Because of the lack of validated questionnaires, Gillespie et al. (2015) used a modified Oral Health Impact Profile-14 (OHIP-14) survey to measure the salivary gland–specific HRQoL after sialendoscopy. The overall modified OHIP-14 scores (mean score 7.8, median score 2) showed that the level of ongoing impairment was relatively mild. Patients with sialoliths had better salivary gland–related QoL compared to patients with non-stone etiology. However, this study also lacks a preoperative evaluation.

In 2015, Aubin-Pouliot et al. (2016b) introduced the Chronic Obstructive Sialadenitis Symptoms (COSS) questionnaire to numerically characterize sialadenitis-specific symptoms experienced by patients at a given point in time and to resolve the impact of these symptoms on daily functions reflecting the HRQoL, such as chewing, speaking, and swallowing, as well as sleeping, daily activities, and emotional symptoms. This self-administered 20-question survey gives a single COSS score from 0–100; a greater COSS score indicates more severe symptoms and disease impact. The COSS questionnaire has proven to be a useful tool in capturing changes in sialadenitis-specific symptoms after sialendoscopy (Aubin-Pouliot et al. 2016a, Delagnes et al. 2017a, Delagnes et al. 2017b), and it has shown that sialendoscopy-assisted salivary duct surgery (SASDS) is effective in reducing symptoms in both sialolithiasis patients and in patients with chronic obstructive sialadenitis without sialolithiasis (Ryan et al. 2019, Plonowska et al. 2019). However, the validity and reliability of the COSS questionnaire need to be assessed in further studies.

3 AIMS OF THE STUDY

The general objectives of this thesis were to study the outcome of the sialendoscopic management of sialolithiasis and sialadenitis, to assess HRQoL and complications related to the sialendoscopic approach, and to evaluate the costs related to the treatment of patients with sialadenitis.

The specific aims were:

1. To study the individual treatment outcome of sialolithiasis, duct stenosis/strictures, and chronic sialadenitis/sialodochitis after sialendoscopic approach.

2. To assess the patient-reported experience and compliance after a sialendoscopy procedure under LA or LAS.

3. To investigate the efficacy of sialendoscopy in the treatment of adult chronic recurrent parotitis and to resolve the possible benefit of a single-dose intraductal steroid injection given concurrently with sialendoscopy.

4. To determine complications related to both diagnostic and interventional sialendoscopy.

5. To assess the HRQoL of patients with recurrent sialadenitis and the possible effects of sialendoscopy on their HRQoL.

6. To assess the hospital costs related to the treatment of patients with recurrent sialadenitis, the sialendoscopy procedure, and the complications of sialendoscopy.

4 PATIENTS AND METHODS

This dissertation consists of five studies. All were conducted at the Department of Otorhinolaryngology – Head and Neck Surgery, HUS, in Helsinki Finland, which is a tertiary-care academic teaching hospital covering about 1.6 million inhabitants.

4.1 Patients

Study I

All patients who underwent sialendoscopy at the Department of Otorhinolaryngology – Head and Neck Surgery, HUS, between January 2011 and December 2013 were retrospectively extracted from the hospital's electronic database. A total of 228 patients (61% female; mean age 46 years, range 4–81; 17 children or adolescents) underwent 266 sialendoscopies and were included in the study. There were 18 patients who underwent bilateral sialendoscopy, and 19 underwent more than one during the study period.

Study II

Patients who underwent sialendoscopy at the Department of Otorhinolaryngology – Head and Neck Surgery, HUS, between March 2012 and December 2013 participated in the study by filling out a questionnaire formulated by the authors. All the patients were operated on by one of the two surgeons performing the most sialendoscopies in the clinic at that point. Patients operated on by other physicians, children under 16 years, patients with insufficient Finnish language skills, patients not able to recruit for the study preoperatively, and patients who underwent the sialendoscopy under GA were excluded. In all, 89 of 132 patients answered the questionnaire and were included (56% female; mean age 50 years, range 16–81). Seven patients underwent bilateral sialendoscopy.

Study III

Fifty-four patients with symptoms of chronic recurrent parotitis not responding to conservative treatment were recruited prospectively at the out-patient clinic of the Department of Otorhinolaryngology – Head and Neck Surgery, HUS, between March 2012 and December 2015. Patient inclusion criteria were at least three prolonged (over 24 hours) or ten shorter episodes of parotid swelling with or without pain during the previous six months and age over 18 years. The exclusion criteria were sialolith(s) detected in preoperative US or MRI or during a sialendoscopy procedure and insufficient Finnish or Swedish language skills. A

total of 49 patients (67% female; mean age 53 years, range 21–75) were included. Five recruited patients were excluded due to spontaneous symptom improvement while waiting for the endoscopy. Eight patients underwent bilateral sialendoscopy.

Study IV

Patients who underwent sialendoscopy at the Department of Otorhinolaryngology – Head and Neck Surgery, HUS, between October 2015 and December 2016 were prospectively recruited for a complication register study. Exclusion criteria were age under 16 years, insufficient Finnish or Swedish language skills, and lack of written informed consent due to failure to prospectively recruit the patients, or patients' refusal from the study. Altogether, 118 of 147 patients (69% female; median age 47 years, range 19–86) with 140 sialendoscopies were included in the study. Fifteen patients underwent sialendoscopy for multiple glands and seven underwent re-sialendoscopy during the study period.

Study V

All patients who underwent sialendoscopy at the Department of Otorhinolaryngology – Head and Neck Surgery, HUS, between January 2014 and May 2016 were extracted from the hospital's electronic database. In all, 260 patients (66% female; mean age 46 years, range 4–86) were found, and the direct hospital costs of those patients covering the time interval of two years (one year prior to sialendoscopy and one year after sialendoscopy) were resolved.

In addition, questionnaires on HRQoL and use of health care services were sent to 188 patients. At baseline, 74 (39%) patients (female 72%; mean age 51 years, range 15–86), after 6 months 60 patients (32%), and after 12 months 56 patients (30%) returned the questionnaires. All three 15D HRQoL questionnaires were returned by 51 patients (27%). Of these patients, 43 (23%) returned the questionnaire concerning the use of primary health care services related to salivary gland disease during the preceding three months. Exclusion criteria were age under 15 years or insufficient Finnish or Swedish language skills. Additionally, some patients were not reached because of changed operation schedules. Twelve patients underwent re-sialendoscopy during the study period.

4.2 Methods

4.2.1 Sialendoscopy

All patients included in the studies underwent sialendoscopy or a sialendoscopy-assisted interventional procedure according to the same protocols. All-in-one sialendoscopes (Karl Storz 11575 A, 11576 and 11573 A) were used. LA, LAS, or GA were used based on the patients' age, co-operation, and expected complexity of the procedure. LA was achieved using a 10% lidocaine-hydrochloride spray and by infiltration of 1% lidocaine with adrenaline under the papilla. After papilla dilatation, 1% lidocaine was administered into the duct. The ductal system was then explored under intermittent lavage with an irrigation solution of 1% lidocaine and 0.9% sodium chloride at a ratio of 1:4. Debris was rinsed out and strictures opened with the help of hydrostatic pressure, the endoscope, a salivary duct probe, a micro drill, or a basket if possible. Sialoliths near the papilla of Wharton's duct were removed via papillotomy, and sialoliths further in the duct with a Dormia basket, if permitted by the size and mobility of the stone. Large or immobile sialoliths were removed by making an incision in the floor of the mouth atop the sialolith. For the parotid gland, an endoscopy-assisted transcutaneous approach with a local skin incision or modified facelift incision was used. After transoral sialolith removal, the wound was left open and no stents or sialodochoplasty were used. After endoscopy-assisted transfacial sialolith removal, the duct, parotid capsule, and skin were closed carefully without stenting. Stents were used only to treat persistent strictures. Prophylactic antibiotics (cefuroxime 1.5 g intravenously intraoperatively, or cephalexin orally for 5–7 days postoperatively) were used under consideration of the surgeon in complicated procedures. Steroid irrigation (1 mL of hydrocortisone, 125 mg/mL) was used in patients with signs of chronic inflammation at the end of the procedure.

4.2.2 Medical records

The medical records of every patient were reviewed and the following information registered: patient demographics, characteristics as well as necessary medical data, comorbidities, American Society of Anesthesiologists (ASA) Physical Status Classification Score, symptoms, symptomatic salivary gland, operated salivary gland, performing surgeon, sialendoscopy findings, type of surgical intervention, operation time, anesthesia, use of antibiotics and corticosteroids, complications, treatment outcome, treatment failure, and further treatments. Patients' general health was assessed using the Charlson Comorbidity Index (CCI) in study IV (Charlson et al. 1987).

The direct hospital costs were obtained from the Ecomed clinical patient administration system (Datawell Ltd, Finland), where all the hospital costs from the Hospital District of Helsinki and Uusimaa are routinely stored. The costs related to the diagnosis and treatment of the patients' salivary gland disease including imaging and laboratory services, outpatient visits, pathology examinations, operations, and inpatient care were calculated. Also, the direct hospital costs related to the possible complications of sialendoscopy were analyzed (study V).

The performed sialendoscopies during the time period of interest were received from the hospital's electronic surgical database, which uses the Finnish nationwide classification of surgical procedures maintained by The National Institute for Health and Welfare and is based on the Nordic Classification of Surgical Procedures (NCSP).

4.2.3 Questionnaires (II, III, V)

In study II, patients completed a questionnaire in which they rated their sensations (level of nervousness before the operation, level of discomfort and pain during the operation, and level of pain after the operation) using a scale of none, mild, moderate, and major. Patients were also asked if they would agree to a new sialendoscopy under LA/LAS later if needed. The questionnaires were filled in after the operation.

In study III, patients filled out a questionnaire in which they estimated the frequency of symptoms during the previous three months and marked the most suitable option from a scale: symptoms weekly, symptoms 2 to 3 times a month, symptoms once a month, symptoms more rarely, and no symptoms. They also rated the severity of symptoms during the previous three months with a visual analogue scale (VAS; horizontal line of 10 cm; 0 = no symptoms, 10 = the worst possible symptoms) by marking the average score on a VAS line. In addition, they estimated the course of the symptoms during the previous three months from a scale: symptom-free, symptoms decreased significantly, decreased slightly, remained unchanged, increased slightly, or increased significantly. The questionnaires were completed before the sialendoscopy and three, six, and twelve months postoperatively.

In study V, the generic 15D HRQoL questionnaire was used. The 15D consists of 15 dimensions, as introduced in chapter 2.8. In each dimension, the respondent chooses one of five levels that best describes their current state of health. The 15D constructs a 15-dimensional profile and a single index score between 0 (equivalent to being dead) to 1 (no problems at any dimension) (Sintonen 2001). The minimal clinically important change or difference in the 15D has been

estimated to be ± 0.015 (Alanne et al. 2015). The age- and gender-matched representative population was obtained from The National Health 2011 Survey (Koskinen et al. 2012).

Also, the self-made questionnaire about the use of health care services related to patients' salivary gland disorders was posted to the patients in study V. In the questionnaire, patients evaluated the number of doctoral visits, nurse's receptions, phone calls, and laboratory services conducted in public or private health care, as well as inpatient treatments and the number of sick leave days required because of salivary gland disorder during the previous three months. The use of services and duration of sick leave were converted into monetary units based on the most recent Finnish data on standard unit costs from 2011 (Kapiainen et al. 2014). Both 15D and the questionnaire on health care services were posted to the patients before sialendoscopy and three and twelve months postoperatively.

4.2.4 Intervention, randomization, and outcomes (III)

Before or during the sialendoscopy, the patients were randomized at a ratio of 1:1 in a double-blind fashion to receive either 1 mL of isotonic saline solution (n=24) or 1 mL of hydrocortisone 125 mg/mL (n=25) intraductally. The study medicine was given to patients after sialendoscopy. Before, the gland was massaged until emptied of the rinsing solution. In cases of bilateral symptoms, sialendoscopy was performed for the gland with more symptoms, and in some cases with equal symptoms, for both glands with an identical technique. Gland massage was recommended from the following day on.

The primary outcome of the study was defined as the efficacy of the sialendoscopy to reduce the symptoms of recurrent parotitis. The secondary outcome was defined as the ability of a single-dose hydrocortisone injection, in conjunction with sialendoscopy, to reduce the symptoms of recurrent parotitis more than sialendoscopy alone. The primary and secondary outcomes, the reduction of symptoms, were based on the symptom frequency as well as severity measured by the VAS.

As this methodology had not been used in prior studies, it was difficult to estimate the average VAS scores and standard deviation (SD) of VAS scores for this patient group, making it challenging to perform accurate power calculations beforehand. As research proceeded, especially the postoperative VAS score proved to be highly variable with high SD, and it revealed that the size of the study group should have been significantly larger to disclose a 20% difference in the postoperative VAS scores between placebo and steroid groups. However, when a 20% decrease in the postoperative VAS score was considered significant for the

primary outcome using 90% power, the whole study population was calculated to be sufficient.

4.3 Statistical analysis

In study I, Pearson's chi-squared test was used to calculate correlations between categorical variables, and the Mann-Whitney U test was used to compare non-normally distributed continuous variables between successful and unsuccessful sialolith removal.

In study II, Pearson's chi-squared test was used to compare categorical variables among patients' answers. Spearman's rank correlation was used to determine the correlations between non-normally distributed variables and patients' answers and the differences of mean systolic and diastolic blood pressures, and the mean pulse between pre- and intraoperative values was determined with a paired sample t-test.

In study III, the Wilcoxon non-parametric signed-rank test was used to determine the difference between symptom frequency and VAS scores before and after sialendoscopy. The Analysis of Covariance Report was used to determine the correlation between categorical variables and VAS change, and Spearman's rank correlation test determined it between continuous non-parametric variables and VAS change. Either Pearson's chi-squared test or Fisher's exact test was used to compare categorical variables between placebo and steroid groups and the independent samples t-test for continuous variables. The frequency of symptoms and VAS scores were compared between placebo and steroid groups using an equal-variance t-test and Analysis of Covariance Report.

In study IV, either Pearson's chi-squared test or Fisher's exact test were used to evaluate the categorical risk factors of complications, and the Equal-Variance t-test evaluated the continuous variables.

In study V, Pearson's chi-squared test or the independent samples t-test was carried out to compare patient characteristics between respondents and non-respondents. The statistical significance of the difference in the mean 15D scores and costs between different groups was analyzed with an independent samples t-test and the significance between baseline and follow-up 15D scores with a paired samples t-test

The NCSS statistical software version 8 (NCSS Inc., Kaysville, UT, USA) or SPSS version 22 (SPSS Inc., Chicago, IL, USA) were used for the statistical analyses. P-values < 0.05 were considered to be significant.

4.4 Ethical considerations

All studies were performed in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines. Written informed consent was obtained from all the patients participating in studies III and IV. In the questionnaire studies II and V, the completion and return of the questionnaires were interpreted as permission to participate in the study. The protocols of studies II, III, IV, and V were approved by the Research Ethics Committee of the HUS. Since study I was retrospective and no patient contacts related to the study were made, ethics approval was not required.

5 RESULTS

5.1 Patients' characteristics (I–V)

The mean age of the patients varied from 46 to 53 years, and the majority of patients were women (61–69%). Studies I and V also consisted of children. In study III, all the patients suffered from chronic recurrent parotitis and, in addition, four patients also had submandibular gland symptoms. In the other studies, a slight majority of patients had submandibular problems (54–56%). About half the sialendoscopies were performed in the parotid glands and half in the submandibular. In studies I and III, the most common symptom was swelling with or without pain in 90–100% of the patients. In addition, 16–29% had suffered from bacterial infections. In study I, 39% of patients had symptoms for less than one year, 37% one to five years, and 23% over five years, while in study III, the mean duration of symptoms was 7.2 years (range 0.5–41).

According to study IV, the majority of sialendoscopy patients were in good health, with only a small number suffering from a severe systemic disease limiting their activity; 45% of patients had an ASA class I, 45% an ASA class II, and 10% an ASA class III, while 55% had CCI 0, 24% had CCI 1, 9% had CCI 2, and 12% had CCI 3 or more. Patients who suffered from chronic recurrent parotitis in study III smoked tobacco more often than patients in study IV. Smoking was not significantly related to any particular diagnosis in study IV ($p=0.48$). Sialadenitis was related to some autoimmune disease in 12 patients (5.3%) in an unselected cohort of 228 patients (study I), and in 6 (12%) patients with chronic recurrent parotitis (study III). The patients' characteristics are presented in Table 3.

Table 3. Characteristics of patients

	Study I	Study II	Study III	Stydy IV	Study V
Patients, n	228	89	49	118	260
Mean age, years (range)	46 (4–81)	50 (16–81)	53 (21–75)	47 (19–86)	46 (4–86)
Gender, n (%)					
Female	138 (61)	50 (56)	33 (67)	81 (69)	171 (66)
Male	90 (39)	39 (44)	16 (33)	37 (31)	89 (34)
Tobacco smoking, n (%)					
Yes, currently	-	-	20 (41)	36 (31)	-
Earlier	-	-	11 (22)	28 (24)	-
No	-	-	16 (33)	51 (43)	-
Unknown	228 (100)	89 (100)	2 (4)	3 (3)	260 (100)
Symptoms, n (%)					
Swelling	206 (90)	-	49 (100)	-	-
Pain	50 (22)	-	19 (39)	-	-
Recurrent bacterial infections	66 (29)	-	8 (16)	-	-
Other	3 (1.3)	-	0 (0)	-	-
Gland, n (%)					
Parotid	106 (46)	43 (48)	49 (100)	53 (45)	114 (44)
Submandibular	122 (54)	46 (52)	0 (0)	65 (55)	146 (56)
Diagnosis, n (%)					
Sialolithiasis	84 (37)	31 (35)	0 (0)	50 (42)	111 (43)
Sialadenitis	112 (49)	42 (47)	49 (100)	45 (38)	129 (50)
Stricture	28 (12)	16 (18)	0 (0)	20 (17)	19 (7.3)
Other	4 (1.8)	0 (0)	0 (0)	3 (2.5)	1 (0.4)

5.2 Sialendoscopy findings and outcomes (I–V)

The most common endoscopic finding in studies I and IV was a sialolith(s) in 37% and 42% of patients, respectively. The second most common finding was inflammatory changes (debris and/or sialodochitis) in 31–32% of patients, while strictures or stenosis were confronted in 23–25%. Normal findings were detected in 17–23% of patients.

In recurrent parotitis, inflammatory changes (mucus plugs or sialodochitis) were detected in 67% of patients and strictures or stenosis in 59%, while 24% of patients had only a small amount of exudate in an otherwise normal ductal system (study III).

The postoperative diagnoses were sialadenitis in 38–50%, sialolithiasis in 35–43%, and stricture in 7.3–18% of the patients (studies I, II, IV, and V). In a few

cases, the postoperative diagnosis turned out to be a disorder not manageable with sialendoscopy, e.g., cysts, sialosis, or unspecific facial pain. Most sialoliths were in the submandibular glands, while the strictures/stenosis and inflammatory changes were more common in the parotid glands. In study III, all patients had diagnosed chronic recurrent parotitis based on the symptoms, imaging, and endoscopy findings, even though strictures and stenosis were common endoscopy finding in this group. The postoperative diagnoses are shown in Table 3.

In study I, the outcome of patients was evaluated at a follow-up visit or by a phone call and ranged based on the main endoscopic finding. The mean follow-up was 18.6 months (range, 0.7–36.2) and 16 (7%) patients were lost in the follow-up. After successful sialolith removal, symptoms resolved in 82% and improved in 13% of patients. In 5%, the symptoms continued the same. Re-sialendoscopy was performed on two patients. After unsuccessful sialolith removal, 50% of patients still reported resolution of symptoms, while in the other 50%, the symptoms did not improve. Five patients underwent submandibulectomy and a combined approach was scheduled for one. The majority of patients with stricture(s) or stenosis reported resolution (40%) or improvement (40%) of symptoms, but in 18% of these patients, the symptoms relapsed during the following months. No improvement was seen in 21% of patients. Four patients needed submandibulectomy, four were scheduled for a re-endoscopy, and nine received corticosteroid intraductally at an outpatient clinic. Symptoms resolved (30%) or improved (56%) in 86% of patients with inflammatory changes as the only finding but relapsed later in 38% of them. Symptoms persisted in 14%. One patient underwent submandibulectomy and the other one Jacobson's neurectomy, two were treated with botulinum toxin injections, and ten with intraductal corticosteroid injections. A re-endoscopy was scheduled for 10 patients. From the patients with normal endoscopic findings, 71% got relief for their symptoms, but the symptoms relapsed later in 12%. No improvement was noticed in 29%. Two patients underwent submandibulectomy, but the symptoms continued after the procedure in the other one, and trigeminal neuralgia or unspecific facial pain was suspected. One patient underwent both botulinum toxin injection and Jacobson's neurectomy, four got corticosteroids intraductally, and one re-endoscopy was scheduled.

In study III, sialendoscopy reduced the symptoms of chronic recurrent parotitis, but the permanent symptom resolution was rare. Both mean VAS score and frequency of symptoms decreased significantly at 3, 6, and 12 months postoperatively ($p<0.001$). At 3 months postoperatively, 27% of patients were symptom-free, symptoms had decreased significantly in 31%, decreased slightly in 20%, remained unchanged in 18%, and increased slightly in 4%. At 12 months

postoperatively, only one (2%) patient had been symptom-free during the whole follow-up time. Patients with higher VAS scores preoperatively had a smaller VAS score change postoperatively (p=0.024), while gender, age, concurrent autoimmune disease, tobacco smoking, teeth status, duration of symptoms, endoscopic finding, or opening of a stricture had no significant impact on the VAS score. Hydrocortisone did not improve the postoperative results significantly when measured by VAS score change or symptom frequency at 3 and 12 months postoperatively.

5.3 Sialoliths (I, IV)

In study I, most sialoliths were over 4 mm in diameter (49/84, 58%; size unknown in 12/84, 14%) ; they were situated most often in the hilar area in the submandibular glands (44/71, 62%) and in the main duct in the parotid glands (6/13, 46%). Of all sialolithiasis patients, 19% (16/84) had more than one sialolith. Sialolith(s) removal was successful in 77% (65/84) of cases. The purely endoscopic sialolith removal was possible only in 23% (19/84) of all cases; 52% (12/23) of sialoliths that were 4 mm or under were endoscopically removable, while the rate was only 8% (4/49) in sialoliths over 4 mm. In three cases with successful endoscopic sialolith removal, the size of the sialolith was not known. Endoscopy-assisted transoral sialolith removal was used successfully in 55% (46/84) of all cases, mostly for sialoliths over 4 mm in diameter and located in the ductal or hilar areas. In three cases, the parotid stone was successfully removed transcutaneously with a combined technique.

Sialolith removal was unsuccessful in 19 cases (23%). Two times, the sialendoscopy-assisted transoral removal of the sialolith failed because of difficult anatomic conditions and multiple sialoliths, and in 17 cases, the endoscopic removal failed because of the adherence of the sialolith. In these cases, a sialendoscopy-assisted transoral approach was not tried mostly due to a hilar or intraglandular sialolith and difficult anatomic conditions, or according to the patient's wishes. A more proximal location of the sialolith was related to unsuccessful sialolith removal (p=0.009), while the size of the sialolith or the duration of the symptoms had no effect on the success rate when noticed in both endoscopic and combined procedures (p=0.42 and p=0.53, respectively). However, the larger diameter of sialoliths (over 4 mm) related significantly more often to unsuccessful endoscopic sialolith removal (p<0.001).

In study IV, sialoliths were eventually successfully removed in 84% (42/50) of patients, with the other 16% (8/50) remaining unsuccessful. Four patients needed a second procedure to ensure the successful removal, so altogether, sialolith removal failed in 12 sialendoscopies (12/54, 22%) during the study period. A

purely endoscopic sialolith removal was successful in only 6 patients (12%), having failed 11 times due to stone adherence. In 36 patients (72%), a sialendoscopy-assisted combined approach was necessary for successful sialolith removal; five of those were sialendoscopy-assisted transcutaneous approaches of parotid stones. One-time sialendoscopy-assisted transoral removal of the submandibular sialolith failed because there were multiple sialoliths and a difficult location.

5.4 Complications (I, IV, V)

A complication was confronted in 15% (21/140) of sialendoscopies in a prospective observational study (IV), and in 8.3% (22/266) in a retrospective study (I). In both studies, the most common complication was an infection in 6.4% (9/140) and 7.1% (19/266) of cases. In study IV, all infections were related to the interventional sialendoscopy, and most occurred in the submandibular glands (8/9, 89%). Sialolithiasis increased the risk of infection significantly (p=0.012), and both a retained sialolith and intraoral stone removal from the posterior region were independent risk factors for the infection (P=.004 and P=.048, respectively) while prophylactic antibiotics in sialolithiasis patients did not decrease the rate of infections (p=0.410). In both studies I and IV, two patients needed intravenous antibiotics and hospitalization, while the others were treated with a peroral course of antibiotics.

All the complications encountered in study IV and the treatment used are represented in Table 4. In all, the risk factors for complications were sialolith removal (p=0.001) and stricture dilatation (p=0.032). Also, longer operation times (p=0.001) and GA (p=0.011) were related to increased complication risk. The surgeon experience, patient age, ASA class, CCI, or tobacco smoking did not correlate with complication risk.

In study V, a complication that caused direct hospital costs occurred in 8.1% of sialendoscopies. The mean hospital cost per complication (€922, SD €1309, range €110–4425) was significantly higher in patients with sialolithiasis (n=16, €1131, SD €1444, range €110–4425) compared to patients with other diagnoses (n=5, €255, SD €130, range €110–435) (p=0.029), and most of the complications were related to the sialolith removal or the attempt.

Table 4. Frequency and treatment of complications of the 140 operated glands; 67 parotid and 73 submandibular glands

Complication	All, n (%)	Parotid, n (%)	Submandibular, n (%)	Treatment
Infection	9 (6.4)	1 (1.5)	8 (11)	Per oral antibiotics (n=7) Hospitalization and intravenous antibiotics (n=2)
Ductal perforation	4 (2.9)	1 (1.5)	3 (4.1)	Normal postoperative care with follow-up (n=4)
Swelling	3 (2.1)	0 (0)	3 (4.1)	Conservative management (n=2) Per oral steroids for 7 days (n=1)
Lingual nerve dysfunction (temporary)	2 (1.4)	0 (0)	2 (2.7)	Analgesics (NSAIDs and paracetamol) with follow-up (n=2)
Basket entrapment	2 (1.4)	2 (3.0)	0 (0)	Removal of entrapped basket and sialolith through transfacial approach (n=2)
Facial nerve dysfunction (temporary)	1 (0.7)	1 (1.5)	0 (0)	Spontaneously resolved within 5 hours (n=1)

5.5 Local anesthesia (II)

LA or LAS was the most common anesthetic method in 89–96% of all sialendoscopies in studies I–V. In study II, 89 patients estimated their postoperative sensations about the LA/LAS procedure, and the answers are presented in Figure 5. According to the ASA depth of sedation scale, 20% of patients had no sedation, 72% had minimal sedation with small doses of fentanyl with or without diazepam, and 8% had moderate sedation with propofol. The mean systolic (135 mmHg vs. 138 mmHg) and diastolic (78 mmHg vs. 84 mmHg) blood pressures of patients were lower during the operation when compared to the preoperative situation ($p=0.039$ and $p<0.001$, respectively), while no significant difference was noticed in the mean pulse (72 bpm vs. 71 bpm) ($p=0.84$). Over half the patients (53%) experienced major or moderate nervousness before the operation. Older patients were less nervous compared to younger ones ($p=0.017$), and men were less nervous than women ($p=0.0012$).

However, the operation was well-tolerated, and the majority of patients estimated the level of discomfort and pain during the operation as mild or none (86% and 89% of patients, respectively). Older patients felt less discomfort compared to younger ones (p=0.036). Patients who underwent sialolith removal through a transoral incision estimated the level of discomfort and pain to be higher than others, but statistical significance was reached only after combining the major and moderate answers (p=0.048 and p=0.053, respectively). The trend for an increased level of pain with longer operation times was observed (p=0.056). After the operation, 87% of patients estimated the level of pain as mild or none, and the majority of patients did not need any pain medicines postoperatively at a hospital. Men experienced less pain than women (p=0.034), and patients whose sialoliths were removed using a transoral incision experienced more pain than others (p=0.016). The majority of patients (97%) would be willing to undergo LA/LAS sialendoscopy again in the future if necessary.

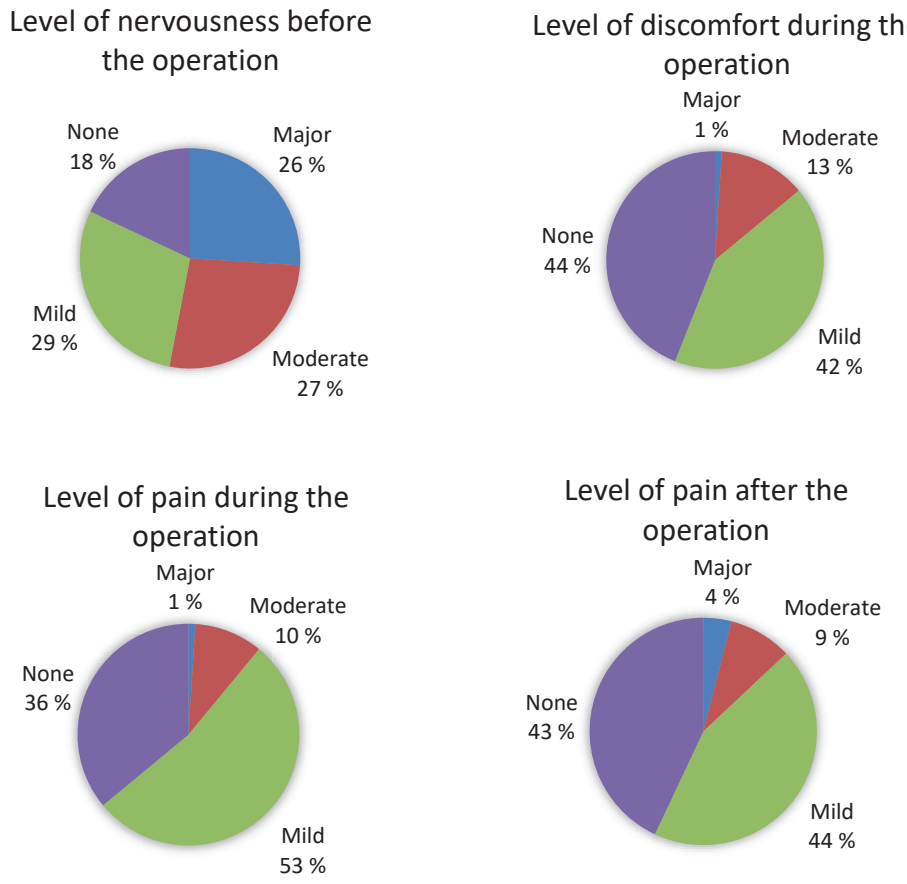

Figure 5 Questions presented to patients after sialendoscopy and patient responses on a scale from major to none.

5.6 HRQoL of patients measured with 15D questionnaire (V)

At the baseline, the mean total HRQoL score of 74 patients was clinically but not statistically significantly lower than that of the age- and gender-matched general population (0.909, SD 0.079 vs. 0.925, SD 0.025, p=0.100). Patients had significantly worse scores on 2 of 16 dimensions: “discomfort and symptoms” (p=0.002) and “distress” (p=0.032). Among the 51 patients who returned all three questionnaires, they had improved in “discomfort and symptoms” at 3 months (p=0.014) and at 12 months (p=0.039) postoperatively significantly, and the total HRQoL score improved in patients with sialolithiasis at 3 months postoperatively (p=0.041). At the 3- and 12-month follow-ups, submandibular gland patients felt less “discomfort and symptoms” compared to parotid gland patients (p=0.022 and p=0.021, respectively). Those with sialolithiasis were less depressed and distressed at baseline (p=0.013 and p=0.035, respectively) and experienced less depression (p=0.002), distress (p=0.006), and discomfort and symptoms (p=0.046) at 3 months postoperatively compared to patients with other diagnoses. The mean 15D profile of patients based on the postoperative diagnosis is presented in Figure 6.

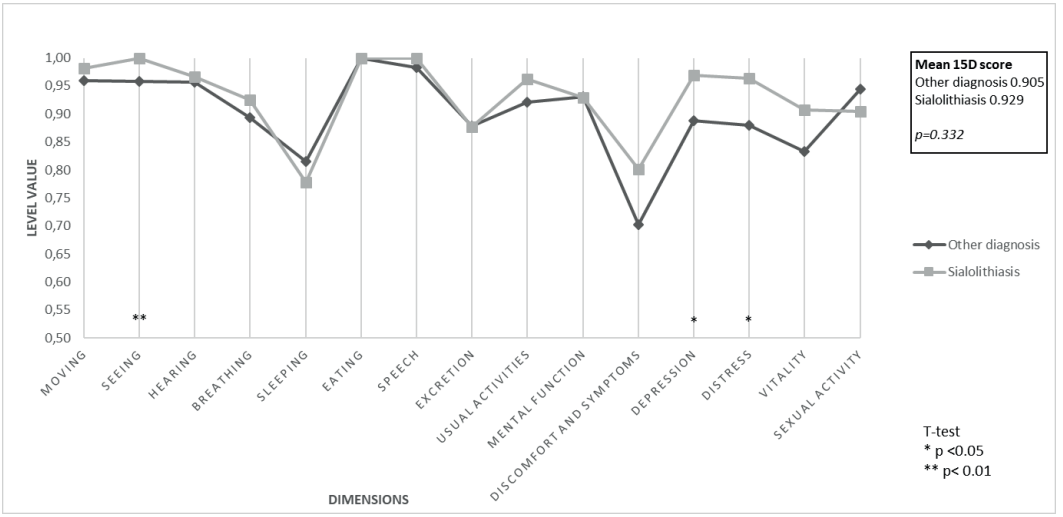

Figure 6a The mean 15D profile of patients with sialolithiasis and other diagnoses before sialendoscopy.

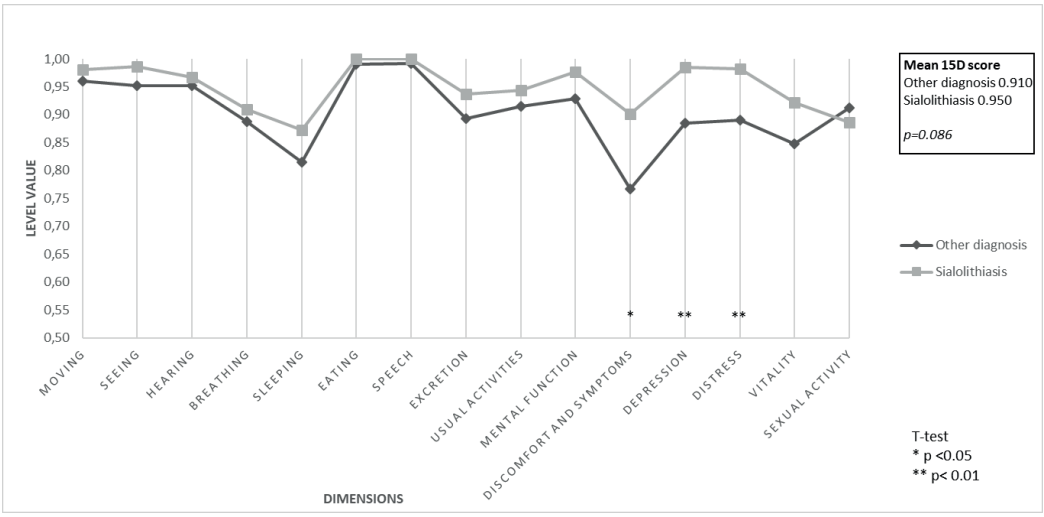

Figure 6b The mean 15D profile of patients with sialolithiasis and other diagnoses at 3 months postoperatively.

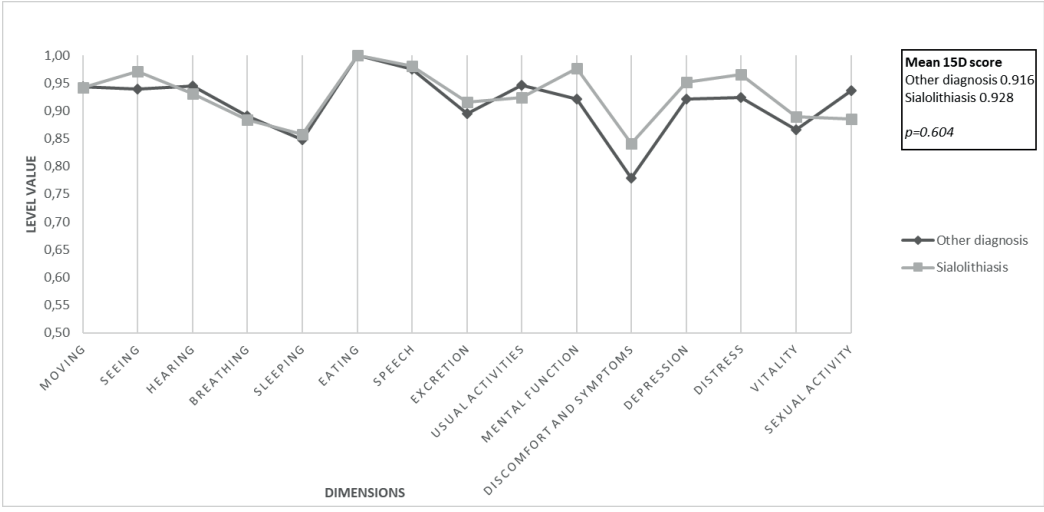

Figure 6c The mean 15D profile of patients with sialolithiasis and other diagnoses at 12 months postoperatively.

5.7 Costs (V)

The mean total hospital costs analyzed from 260 patients during the two-year time period (one year prior to sialendoscopy and one year after sialendoscopy) were €2265 per patient (SD €968, range €1280–7880), the mean costs of the sialendoscopic-procedure(s) were €1673 per patient (SD €466, range €1170–4373; €1593 per procedure), and the mean costs of the clinical encounters (also containing phone contacts and laboratory and imaging costs) were €416 per patient (SD €378, range €0–2215). The mean total hospital costs, mean costs of sialendoscopy, and mean costs of complications were statistically significantly higher among patients with sialolithiasis compared to patients with other postoperative diagnoses (p=0.014, p<0.001 and P=0.029, respectively), while the mean costs of the clinical encounters were higher in patients without sialoliths (p=0.012). Submandibular gland patients had higher sialendoscopy-related costs (p=0.006), but the costs of clinical encounters (p=0.006) were lower when compared with parotid gland patients (Figure 7).

The questionnaire concerning the use of primary health care services related to salivary gland disease during the preceding three months revealed that a significant decrease in the mean total costs occurred from baseline to 12 months postoperatively (p=0.001), and from the individual costs of doctor visits in private or public primary health care, hospital costs and the costs of other contacts decreased significantly from baseline to 12 months postoperatively (p<0.01) among 43 respondents.

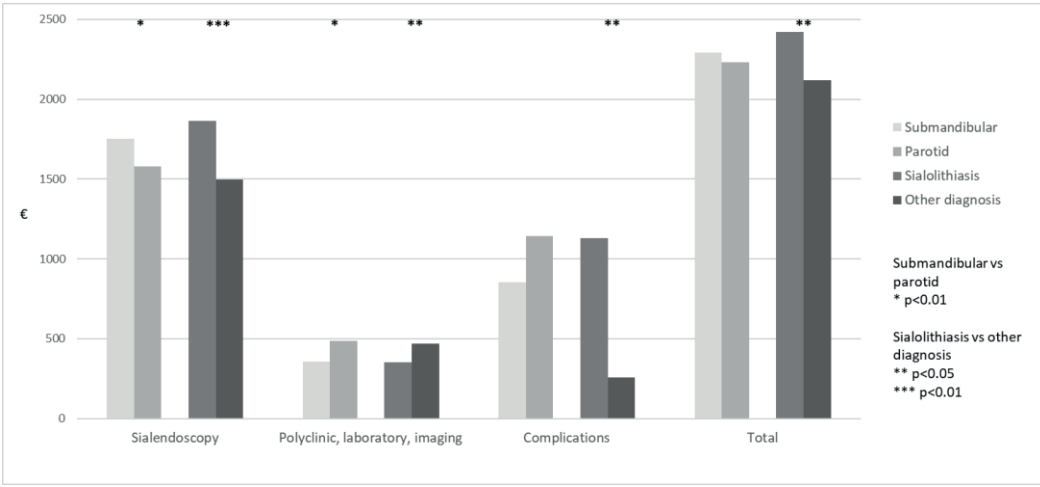

Figure 7 Hospital costs.

6 DISCUSSION

6.1 Sialendoscopy findings and outcomes (I, III, IV)

The most common endoscopic findings (studies I and IV) were sialolithiasis followed by inflammatory changes and strictures or stenosis. Sialoliths were more frequent in the submandibular glands, whereas stenosis, strictures, mucus plugs, and signs of sialodochitis existed more often in parotid glands, which is in line with other studies (Chuangqi et al. 2013, Gallo et al. 2016). Ductal strictures or stenosis are the second-most frequent cause of obstruction in the salivary glands, especially seen in cases of unclear swelling (Ngy et al. 2007, Gillespie et al. 2011, Vashishta & Gillespie 2013). In many cases, strictures or stenosis occur together with inflammatory changes and are related to the chronic inflammatory process (Nahlieli et al. 2006a).

The most frequent endoscopic findings in chronic parotitis were mucus plugs followed by strictures with or without dilatation of the duct, stenosis, and sialodochitis. A pale matte appearance of the duct with mucus plugs and strictures or stenosis has been described in both adults and children with chronic parotitis (Nahlieli et al. 2004a, Shacham et al. 2009). Sialendoscopy findings confronted in our study in different salivary gland disorders are shown in Table 5.

In total, 17–24% of our patients did not have any specific endoscopic findings, except for a small amount of exudate in some cases. This is more than in many previous studies (Koch et al. 2005, Chuangqi et al. 2013, Vashishta & Gillespie 2013). This might be due to less severe disease in some patients or it may be the interpretation of the surgeon. The majority of these patients (71%), however, benefitted from the sialendoscopy (study I). In these cases, simply the dilatation of the duct might have helped, and in some cases, there might have been a placebo effect.

Treatment of ductal strictures and stenosis endoscopically or with an endoscopy-assisted transoral approach has high success rates of 80–100%, with improvement of symptoms in 75–95% of cases (Nahlieli et al. 2001, Ardekian et al. 2010, Koch et al. 2012a, Koch et al. 2012b, Kopec et al. 2013b). However, most patients report some degree of persistent symptoms or recurrence of symptoms postoperatively, which is in line with our results (Koch et al. 2014, Delagnes et al. 2017b); over 60% of stricture/stenosis patients had some postoperative symptoms, and recurrences occurred in 18% (study I). Unlike in many other studies, we did not have balloon dilators available, and we did not use transoral surgery for strictures, excluding papillotomy.

In study I, 70% of patients with inflammatory changes had continuous symptoms postoperatively, even though mostly to a lesser degree, and 38% had a

relapse of symptoms (study I). However, contrarily, 86% had a resolution or some improvement of their symptoms, which is comparable to the literature (Vashishta & Gillespie 2013).

In study III concerning chronic recurrent parotitis, 78% of patients got some relief for their symptoms three months postoperatively. For the rest, the symptoms remained unchanged or increased. Patients with more severe preoperative symptoms received less benefit from the sialendoscopy, which might be explained by more aggressive or advanced disease. We did not find any significant benefit from a ductal single-dose steroid given after sialendoscopy compared to sialendoscopy with saline irrigation only. However, few studies have suggested that sialendoscopy followed by repeated ductal steroid irrigations might produce a better outcome than sialendoscopy alone in patients with chronic inflammation (Capaccio et al. 2017, Capaccio et al. 2018a). In a study of SS patients, no significant difference was found between sialendoscopy and sialendoscopy+steroid groups on salivary flow and xerostomia (Karagozoglu et al. 2018).

Table 5. Sialendoscopy findings in different salivary gland disorders

Disorder	General sialendoscopy findings	Other possible sialendoscopy findings
Chronic sialadenitis (e.g., chronic recurrent parotitis/JRP/RAI-induced sialadenitis/Sjögren's syndrome)	mucus plugs/fibrinous exudate, a pale, avascular matte appearance of the duct, strictures and/or stenosis of the duct, irregular enlargement or dilatation of the duct	erythematous/irrigated duct with small ecchymosis, atrophic ducts
Obstructive sialadenitis	adhesive or floating sialolith, stricture or stenosis of the duct, mucus plugs	kink of the duct, polyp
Duct stricture	a short, web-like or fibrotic segment of intraductal narrowing/scar, complete blockage of the duct	local dilatation of the duct, mucus plugs/exudate
Duct stenosis	a long/diffuse narrowing of the ductal lumen	local dilatation of the duct, mucus plugs/exudate

6.2 Sialoliths (I, IV)

In our study, most submandibular stones were located in the hilar area, while parotid stones were more often found in the main duct, which is in line with the literature (Yu et al. 2010, Zenk et al. 2012, Schwartz et al. 2015a, Kondo et al. 2018). In our studies, the sialoliths were successfully removed with an interventional sialendoscopy or with incisional sialolithotomy in 77–84% of cases, but only in 12–23% of cases, the removal was possible purely endoscopically. In the literature, the overall success rates, from 76–95%, have been published depending on the study population, experience of surgeons, and available instrumentation (Combes et al. 2009, Yu et al. 2010, Bowen et al. 2011, Liu et al. 2013, Pace et al. 2014, Schwartz et al. 2015a, Kopec et al. 2016, Schapher et al. 2017). Reported success for endoscopic sialolith removal varies between 29% and 89%, which is higher than in our findings (Nahlieli et al. 2006a, Papadaki et al. 2008, Yu et al. 2010, Bowen et al. 2011, Luers et al. 2011, Kopec et al. 2016). However, in many studies, the instrumentation includes lasers or intraductal lithotripters, which were not available in our studies (Nahlieli et al. 2006a, Papadaki et al. 2008).

A large study of more than 1000 sialolithiasis patients showed that only 5% of submandibular and 22% of parotid sialoliths were removable purely endoscopically with a basket, miniature drill, or forceps (Zenk et al. 2012). In another study, 13% of submandibular stones and 38% of parotid stones were successfully removed with interventional sialendoscopy alone, while the rest required incisional sialolithotomy or gland excision, which is consistent with our results (Fabie et al. 2019). The size limit for successful endoscopic stone removal is considered to be 3–5 mm. Generally, stone crushing of some form is needed for larger stones (Marchal & Dulguerov 2003, Zenk et al. 2012).

The most common causes for unsuccessful sialolith removal were adherence of the sialolith and proximal location. The prognostic factors for successful endoscopic removal of a sialolith are small size, good mobility, round or oval shape, and distal location (Luers et al. 2011, Cox et al. 2018). In Figures 8 and 9, a decision tree is presented for the management of parotid and submandibular salivary stones according to diameter and position of the stone based on our studies and previous literature. We have used endobuccal transmucosal duct incision for the removal of distal parotid stones, but some authors refrain from that in fear of duct stenosis (Witt et al. 2012). ESWL has been used successfully for the treatment of impacted sialoliths in both the submandibular and parotid glands (Escudier et al. 2010, Zenk et al. 2012), but it is not mentioned in our figure because ESWL is not available in Finland.

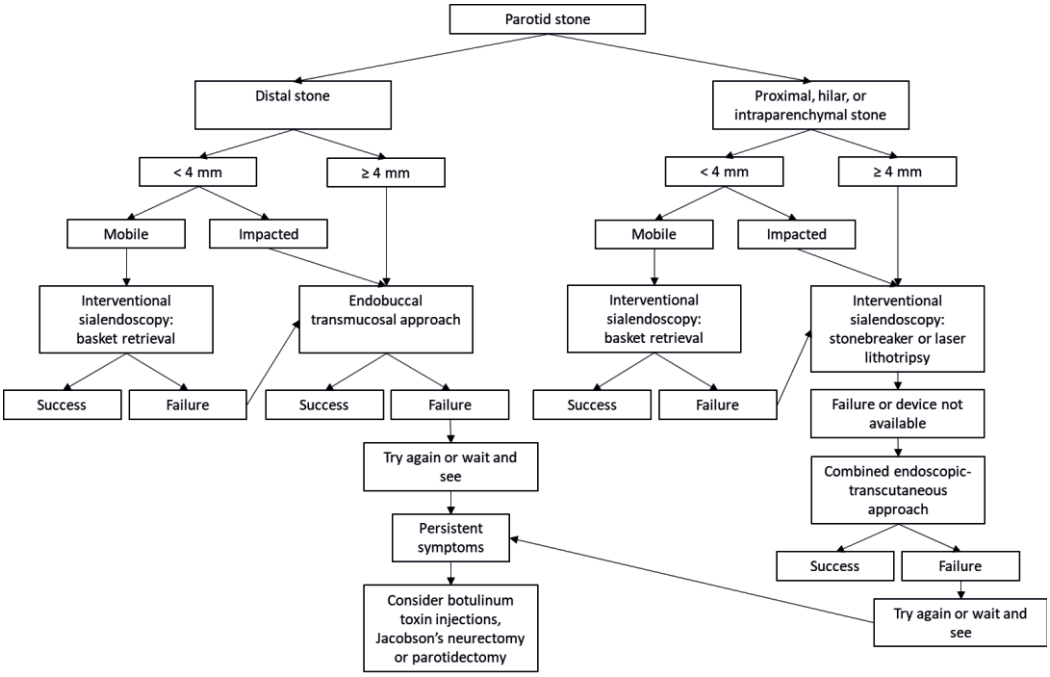

Figure 8 Decision tree for the best minimally invasive treatment of the parotid stones based on our study and literature.

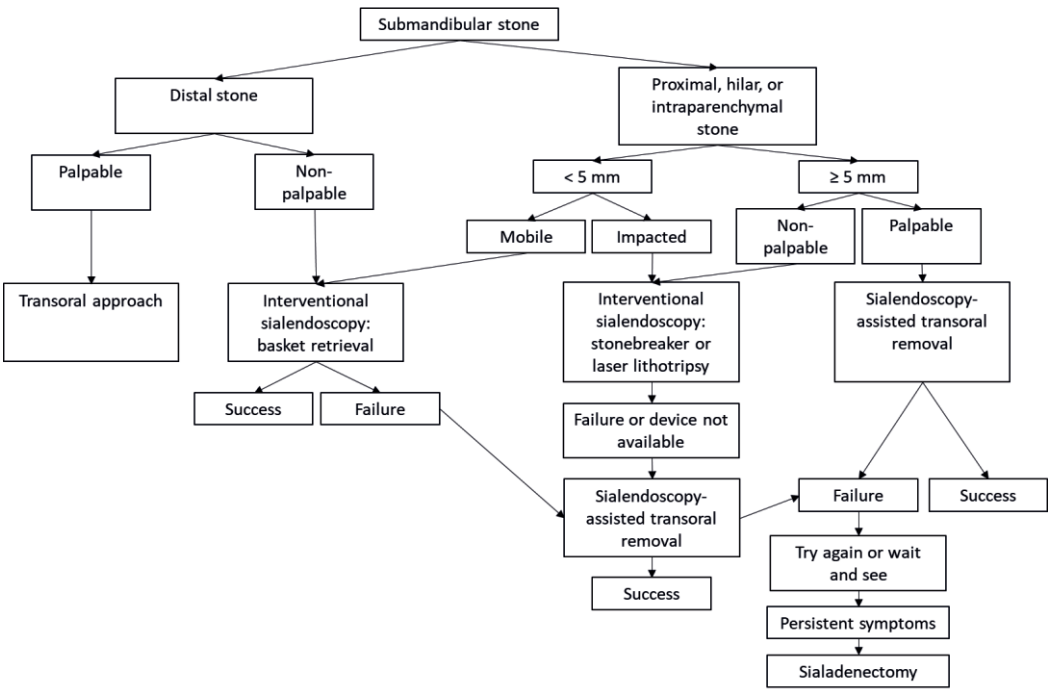

Figure 9 Decision tree for the best minimally invasive treatment of submandibular stones based on our study and literature.

6.3 Complications (I, IV, V)

The complication rates for sialendoscopy and sialendoscopy-assisted operations range from 2–15%, being around 3–5% in larger series (Koch et al. 2005, Gillespie et al. 2011, Felton et al. 2012, Rasmussen et al. 2012, Nahlieli 2015, Gallo et al. 2016). In some studies, failure to perform an intervention is defined as a complication, increasing the complication rates as high as 20–30% (Walvekar et al. 2008, Karagozoglu et al. 2017). According to the Clavien-Dindo Classification of Surgical Complications, failure to treat is not counted as a complication (Dindo et al. 2004). We used this definition in our prospective complication study. The relatively high rate of complications (15%) confronted in our fifth study might be related to the prospective setup, where all the complications were defined and prospectively registered before the study. In addition, the registration of postoperative swelling as a complication varies. Swelling of the gland is a natural reaction for the irrigation and usually resolves after a few hours to a few days (Nahlieli & Baruchin 2000, Koch et al. 2005). We classified postoperative swelling as a complication if it required treatment or was prolonged, but in many studies, it is probably not registered as a complication at all.

The most common complications in sialendoscopy are perforations or strictures of the duct (Nahlieli et al. 2006a, Rasmussen et al. 2012, Nahlieli 2015, Gallo et al. 2016, Karagozoglu et al. 2017). In our study, postoperative infections were the most ruling (6–7%), while stricture was confronted only once (study I). However, strictures may be underdiagnosed since re-sialendoscopy was not performed on all patients with persistent symptoms.

Postoperative infections were significantly associated with sialoliths. Sialendoscopy-assisted transoral sialolith removal from the posterior region and retained sialoliths after an unsuccessful removal attempt both predisposed to infections. In other studies, postoperative infection rates between 0% and 11% have been reported, mostly around 1% (Rasmussen et al. 2012, Nahlieli 2015, Gallo et al. 2016, Karagozoglu et al. 2017). Both pre- and postoperative antibiotics are widely used in sialendoscopy, and some authors also use postoperative steroids (Koch et al. 2005, Nahlieli et al. 2006a, Liu et al. 2009, Strychowsky et al. 2012, Nahlieli 2015). Interestingly, we found no association between prophylactic preoperative antibiotics and the rate of infections. One explanation may be the postoperative swelling of the duct with salivary stagnation, which might predispose to infection. To determine whether the use of antibiotics and/or steroids reduces the rate of postoperative infections in interventional endoscopies, more randomized, controlled studies are needed. We do not recommend routine antibiotics or corticosteroids after diagnostic sialendoscopies since practically no postoperative infections were noted in this group.

Other complications confronted in our studies were transient lingual nerve paresthesia, ranula formation, basket entrapment, salivary fistula, and temporal weakness of the marginal branch of the facial nerve. They were also associated with interventional endoscopies in most cases. Permanent lingual nerve paresthesia after transoral submandibular sialolith removal, as well as lingual nerve damage during purely intraductal endoscopic procedures, are very rare (Nahlieli 2009, Gallo et al. 2016). In addition, ductal avulsion (Walvekar et al. 2008), hemorrhage (Nahlieli et al. 2006a), sialoceles (Carta et al. 2017), and extravasation of the irrigation fluid leading to the pharyngeal swelling and airway obstruction (Papadaki et al. 2008, Martins-Carvalho et al. 2010) have been reported but not encountered in our studies.

The costs of complications varied widely in study V with higher costs related to sialolithiasis. The need for an inpatient treatment or re-operation(s) among some patients with infection, salivary fistula, or ranula increased the costs significantly.

6.4 Tolerability of sialendoscopy (II)

The type of anesthesia depends on many factors, such as invasiveness of the operation, the surgeon's personal preferences, site and painfulness of the surgery, and patient-dependent factors. The patient's compliance is the key to the success of LA or LAS. In sinonasal surgery, LA/LAS was associated with shorter operation time, faster patient recovery, and shorter hospital stay when compared to GA procedures (Fedok et al. 2000, Daskaya et al. 2014). In addition, the side effects of GA can be avoided in LA and LAS.

Our study shows that sialendoscopy is well tolerated in adult patients under LA/LAS with only minimal experience of pain and discomfort. Similar results have been reported in a few other studies assessing patients' satisfaction after LA/LAS sialendoscopy (Luers et al. 2012b, Bawazeer et al. 2018). Patients experienced more pain and discomfort during the operation and postoperatively if the sialolith was removed via a transoral incision. However, almost all patients (97%) agreed to a new LA/LAS procedure if necessary. In other studies, patients have also favored LA/LAS over GA (Knezevic et al. 2012). While LA can give a patient a sense of control during the procedure, others can regard the idea of LA as very stressful and unpleasant. During the study period, six patients (4.5%) had major anxiety regarding the operation, and they requested a GA procedure. A GA procedure was also planned in advance for seven sialolith patients whose procedures were expected to be complex and long, which might have caused some bias in the study outcome. The operative success rate and outcome seem equal in

LA/LAS and GA procedures (Bawazeer et al. 2018). In our study, the operation time was shorter in LA/LAS procedures, while Bawazeer et al.'s (2018) study showed the contrary. However, in our study, more complex procedures were performed under GA than under LA/LAS. We excluded children from this study, but Konstantinidis and colleagues (2011) showed that diagnostic sialendoscopy can be performed under LA in children older than 8 years of age.

The advantage of LA/LAS is that the personnel can tailor the degree of anesthesia to the needs of the patients. Most of the patients (72%) got a small dose(s) of fentanyl perioperatively, which was given to patients if any inconvenience or pain was detected. This might explain the decrease of mean systolic and diastolic blood pressure in patients, but it can also be noted in the rather low level of patient arousal and pain during the operation.

6.5 HRQoL after sialendoscopy (V)

We used a generic, self-administered, 15D HRQoL instrument in study V. Although no statistically significant difference was observed in the 15D score between the patients and the general population before the sialendoscopy, the difference was over 0.015, which has been estimated to be the minimal clinically important change, so it could be estimated that the HRQoL of patients with sialadenitis is slightly decreased when compared to the matched general population (Alanne et al. 2015). The overall HRQoL improved significantly only in patients with sialolithiasis at three months postoperatively, but not in others. In comparison, tonsillectomy patients had significantly decreased HRQoL when compared to the general population, and their HRQoL improved after tonsillectomy (Wiksten et al. 2013), while septoplasty patients had slightly better HRQoL than the general population preoperatively, and the HRQoL decreased after septoplasty based on the 15D questionnaire (Hytonen et al. 2012). However, the patient selection cannot be underestimated in surgical procedures since the HRQoL of septoplasty patients has shown to increase after septoplasty in other studies with more severe preoperative symptoms (Alakärppä et al. 2017).

The subgroup analysis preoperatively and at three months postoperatively revealed that ailments in sialolithiasis patients may be less burdensome and the sialendoscopy more effective than in patients with other etiologies, which has also been noticed in other studies concerning HRQoL (Meier et al. 2015, Gillespie et al. 2015, Aubin-Pouliot et al. 2016b). This is not surprising, since the symptoms usually resolve after successful sialolith removal, while the patients with chronic sialadenitis, strictures, or stenosis have persistent or recurrent symptoms more often (Achim et al. 2017). However, unexpectedly, the HRQoL of sialolithiasis patients decreased again at 12 months postoperatively. This could be because of

only partial success in the sialolith removal in some patients, concurrent inflammatory disease, and/or the stenosis or appearance of other diseases or problems in some patients. Ryan et al. (2019) could demonstrate a durable, long-term benefit from SASDS for sialolithiasis patients with both endoscopic and open techniques with only minor residual symptoms. Unlike the study by Meier et al. (2015), our results suggest that the parotid patients have more discomfort and symptoms postoperatively compared to submandibular patients. This may relate to the higher incidence of chronic inflammation and strictures in parotid glands.

The 15D questionnaire failed to demonstrate any significant difference in dimension eating, even though the patients with obstructive sialadenitis could be assumed to have problems in this area. However, in the 15D questionnaire, this dimension measures the mechanical aspect of eating rather than symptoms while eating.

6.6 Costs of sialendoscopy (V)

Only a few studies have concerned the costs and cost-effectiveness of sialendoscopy (Shashinder et al. 2011, Rosbe et al. 2015, Ong et al. 2017, Kowalczyk et al. 2018). The mean cost of sialendoscopy (€1673) comprised a substantial part of the mean total hospital costs (€2265) of treated patients during the two-year time period in our study. The sialolithiasis patients needed more GA, overnight stay at a hospital, or a second endoscopic procedure to ensure successful stone removal, and a higher rate of complications was encountered within these patients, which explains the higher costs of care and sialendoscopy within this group. The mean costs of clinical encounters were higher in patients without sialoliths as well as in parotid patients, which might be related to the over-representation of chronic sialadenitis with ongoing symptoms requiring ambulatory interventions.

We were not able to assess the cost-effectiveness of sialendoscopy since we did not have a control group in our study. Few retrospective studies have tried to estimate this. According to Rosbe et al. (2015), the treatment of JRP is much more expensive with sialendoscopy than with conservative treatment with the same results, while Ong et al. (2017) deduced that the costs of transfacial sialendoscopy-assisted removal of parotid sialoliths were much lower and the procedure much faster than parotidectomy. However, since in Finland a parotidectomy is rarely performed because of sialolithiasis nowadays, a more appropriate and interesting benchmark would be conservative treatment, Jacobson's neurectomy, or botulinum toxin therapy. In our study, the sialendoscopy-assisted treatment of sialolithiasis (mean cost €1863) was less expensive compared to the

submandibulectomy (mean cost €2293). Shashinder et al. (2011) estimated that the most cost-effective treatment of sialolithiasis is a polyclinic transoral sialolith removal, but the study lacked a control group.

In our study, most procedures were performed in a fully equipped operating theater, but a few took place in a smaller polyclinical operating room. According to Coniglio et al. (2019), in-office–based sialendoscopy might reduce the time burden and health care charges of patients compared to the operating theater procedure.

6.7 Limitations of the study

Since the study I was retrospective, some medical records were insufficient and lacked the surgeon's opinion about the main endoscopic findings. Also, some follow-up data were lost.

In study II, the lack of a validated questionnaire made comparing our results to other studies and surgical procedures difficult. In addition, since the study protocol was not randomized, we could not compare the LA/LAS sialendoscopies to GA ones and find the best anesthetic method.

Study III lacked a true control group. Both study groups underwent a procedure, and a placebo effect is always possible after an intervention. A lack of a validated symptom outcome questionnaire can also be seen as a limitation, and an assessment of symptoms during the last three months may lead to some memory bias. We were able to recruit only a limited number of patients due to the relatively low rate of patients with chronic recurrent parotitis, and the number of patients was not sufficiently powered to determine a clinical difference between the steroid and non-steroid groups, which may cause a false-negative result (type II error).

In study IV, the relatively small study population and lack of routine control visits were the main limitations. However, the patients got thorough information about the normal postoperative recovery and symptoms of common complications and were engaged to contact the emergency department of our hospital if they suspected any deviation from normal recovery.

In study V, the patients' response rate was disappointingly low, which may lead to over- or under-representation of patients whose HRQoL was impaired because of recurrent sialadenitis. Moreover, the lack of a control group and validated salivary gland–specific HRQoL questionnaire can be seen as a limitation.

6.8 Future aspects

Nowadays, the focus of the treatment of salivary glands' obstructive and inflammatory pathologies is to preserve the gland and its function with minimally invasive methods. This reflects the wider trend in surgery, which, with the help of improved optical technologies combined with smaller and less invasive incisions, is focused on improving function and speeding up the recovery. A growing interest against endoscopic and other minimally-invasive approaches to treat benign salivary gland disorders is detected worldwide. As this improves the treatment opportunities in many cases, the right patient selection becomes more important in helping to keep the growing health care costs in control and to get the best benefit from the new treatment methods. Thus, the efficacy and cost-effectiveness of sialendoscopy and sialendoscopy-assisted operations in different patient groups with prospective, controlled studies are definitely worth future studies. Furthermore, many procedure-related issues and guidelines still need to be examined with no consensus existing, e.g., regarding appropriate anesthesia, the role of prophylactic antibiotics, stents, or corticosteroids in sialendoscopy.

In turn, the development of imaging methods permits more accurate diagnostics, making the preoperative planning easier. MR virtual endoscopy seems to be an effective and noninvasive diagnostic method for evaluating the endoluminal anatomy and pathologies of the salivary duct (Su et al. 2006), and combined CT navigation and the sialendoscopy-assisted approach have been used successfully in the removal of deep intraparenchymal, nonpalpable, and impacted parotid stones (Capaccio et al. 2018). Although this means more technical efforts and costs, it can be an acceptable solution for selected patients and also a cost-effective treatment compared to traditional surgery or conservative treatment with decades of persisting symptoms.

In Figure 10, we present an algorithm for the modern treatment of salivary gland swelling based on our experience and literature.

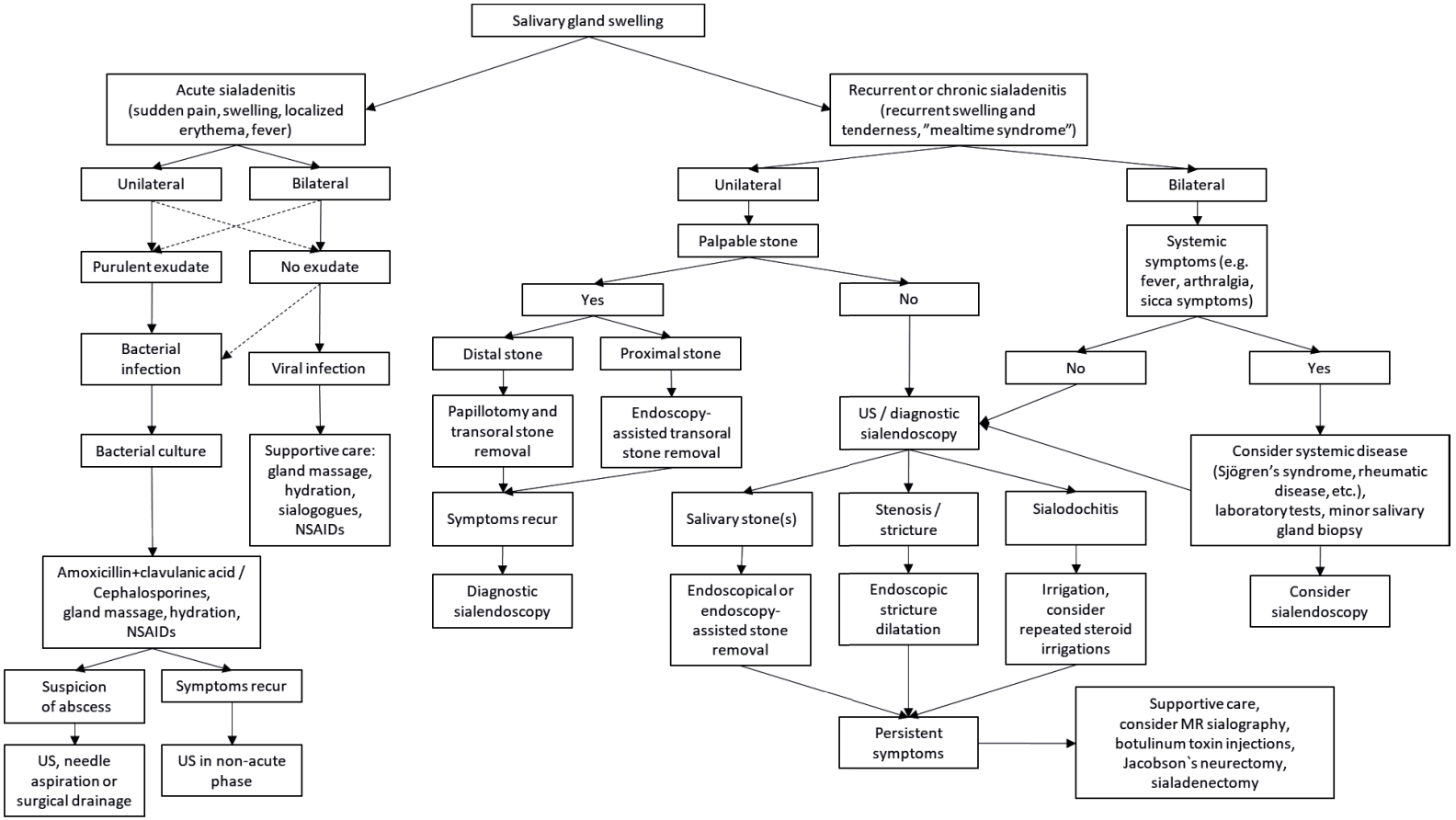

Figure 10 An algorithm for the treatment of salivary gland swelling.

7 CONCLUSIONS

1. Endoscopic stone removal is usually possible with a basket only if the stone is mobile and its diameter is under 5 mm. In cases of larger or attached stones, the crushing or combined approach is needed for successful removal. Sialendoscopy improves the symptoms of chronic sialadenitis and strictures/stenosis, but some residual symptoms are common and recurrences happen often.

2. Most sialendoscopies can be performed under LA/LAS with low patient discomfort and pain.

3. Sialendoscopy effectively reduces the symptoms of chronic recurrent parotitis in adults. A single-dose steroid injection concomitant to sialendoscopy provided no additional benefit for the symptoms of chronic recurrent parotitis in this study.

4. Complications of sialendoscopy are usually related to interventional sialendoscopy. Although most complications are minor, they may necessitate multiple patient contacts, further treatments, or hospitalization. The most common complication in this study was postoperative infection.

5. Sialendoscopy improved the HRQoL only in sialolithiasis patients at the three-month follow-up when assessed with the 15D questionnaire.

6. Sialendoscopic or sialendoscopy-assisted treatment of patients with sialolithiasis was more expensive than the sialendoscopic treatment of patients with strictures/stenosis and sialadenitis during the two-year time period.

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Johanna Jokela

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APPENDICES

Appendix 1. Questionnaire of tolerability of sialendoscopy under LA/LAS, study II

The surgeon fills:

LA / LAS / GA

Parotid gland / submandibular gland sin / dx / la

Were there any interventions performed? If so, what?

What anesthetics were used?

The patient fills:

Gender: woman / man

Age:

Have you had an endoscopy of the salivary gland before?

If yes, how many times?

Before the operation, the level of nervousness I felt was:

a. major
b. moderate
c. minor
d. none

After the operation, the pain I felt was:

a. major
b. moderate
c. minor
d. none

During the operation, the discomfort I felt was:

a. major / discomfort all the time
b. moderate / discomfort at times
c. minor / discomfort a few times
d. none / I did not feel discomfort at all

During the operation, the pain I felt was:

a. major
b. moderate
c. minor
d. none

I would **agree / disagree** to another operation again under local anesthesia, if necessary.

Appendix 2. Multiple-choice questionnaire, study III

1. How long ago did the parotid gland swell for the first time? _____

2. How long did it take before the parotid gland swelled the second time? _____

3. Parotid symptoms during the last 3 months:
   a. Once a week or more often
   b. 2 to 3 times a month
   c. Once a month
   d. More rarely
   e. No symptoms

4. Parotid symptoms during the last 6 months:
   a. Once a week or more often
   b. 2 to 3 times a month
   c. Once a month
   d. 3 to 5 times during the last 6 months
   e. More rarely
   f. No symptoms

5. Parotid symptoms during the last year:
   a. Once a week or more often
   b. 2 to 3 times a month
   c. Once a month
   d. 3 to 5 times during the last 6 months
   e. More rarely
   f. No symptoms

6. Symptoms have been all the time:
   a. Only on the right side
   b. Only on the left side
   c. More on the right side, but also on the left side
   d. More on the left side, but also on the right side
   e. Equally on both sides

7. Symptoms have been during the last 6 months:
   a. Only on the right side
   b. Only on the left side
   c. More on the right side, but also on the left side
   d. More on the left side, but also on the right side
   e. Equally on both sides

8. During the last 3 months, the symptoms have:
   a. Finished
   b. Decreased significantly
   c. Decreased slightly
   d. Remained unchanged
   e. Increased slightly
   f. Increased significantly

9. Estimate how severe the parotid symptoms have been <u>during the last 3 months</u>? Please mark on the line below the point that best represents your perception.

|----------|
No symptoms at all — The worst possible symptoms

Appendix 3. The 15-dimensional measure of health-related quality of life (15D), study V

Please read through all the alternative responses to each question before placing a cross (x) against the alternative which best describes your present status. Continue through all 15 questions in this manner, giving only one answer to each.

Question 1. Mobility
1 ( ) I am able to walk normally (without difficulty) indoors, outdoors and on stairs.
2 ( ) I am able to walk without difficulty indoors, but outdoors and/or on stairs I have slight difficulties.
3 ( ) I am able to walk without help indoors (with or without an appliance), but outdoors and/or on stairs only with considerable difficulty or with help from others.
4 ( ) I am able to walk indoors only with help from others.
5 ( ) I am completely bed-ridden and unable to move about.

Question 2. Vision
1 ( ) I see normally, i.e. I can read newspapers and TV text without difficulty (with or without glasses).
2 ( ) I can read papers and/or TV text with slight difficulty (with or without glasses).
3 ( ) I can read papers and/or TV text with considerable difficulty (with or without glasses).
4 ( ) I cannot read papers or TV text either with glasses or without, but I can see enough to walk about without guidance.
5 ( ) I cannot see enough to walk about without a guide, i.e. I am almost or completely blind.

Question 3. Hearing
1 ( ) I can hear normally, i.e. normal speech (with or without a hearing aid).
2 ( ) I hear normal speech with a little difficulty.
3 ( ) I hear normal speech with considerable difficulty; in conversation I need voices to be louder than normal.
4 ( ) I hear even loud voices poorly; I am almost deaf.
5 ( ) I am completely deaf.

Question 4. Breathing
1 ( ) I am able to breathe normally, i.e. with no shortness of breath or other breathing difficulty.
2 ( ) I have shortness of breath during heavy work or sports, or when walking briskly on flat ground or slightly uphill.
3 ( ) I have shortness of breath when walking on flat ground at the same speed as others my age.
4 ( ) I get shortness of breath even after light activity, e.g. washing or dressing myself.
5 ( ) I have breathing difficulties almost all the time, even when resting.

Question 5. Sleeping
1 ( ) I am able to sleep normally, i.e. I have no problems with sleeping.
2 ( ) I have slight problems with sleeping, e.g. difficulty in falling asleep, or sometimes waking at night.
3 ( ) I have moderate problems with sleeping, e.g. disturbed sleep, or feeling I have not slept enough.
4 ( ) I have great problems with sleeping, e.g. having to use sleeping pills often or routinely, or usually waking at night and/or too early in the morning.
5 ( ) I suffer severe sleeplessness, e.g. sleep is almost impossible even with full use of sleeping pills, or staying awake most of the night.

Question 6. Eating
1 ( ) I am able to eat normally, i.e. with no help from others.
2 ( ) I am able to eat by myself with minor difficulty (e.g. slowly, clumsily, shakily, or with special appliances).
3 ( ) I need some help from another person in eating.
4 ( ) I am unable to eat by myself at all, so I must be fed by another person.

5 ( ) I am unable to eat at all, so I am fed either by tube or intravenously.

Question 7. Speech
1 ( ) I am able to speak normally, i.e. clearly, audibly and fluently.
2 ( ) I have slight speech difficulties, e.g. occasional fumbling for words, mumbling, or changes of pitch.
3 ( ) I can make myself understood, but my speech is e.g. disjointed, faltering, stuttering or stammering.
4 ( ) Most people have great difficulty understanding my speech.
5 ( ) I can only make myself understood by gestures.

Question 8. Elimination
1 ( ) My bladder and bowel work normally and without problems.
2 ( ) I have slight problems with my bladder and/or bowel function, e.g. difficulties with urination, or loose or hard bowels.
3 ( ) I have marked problems with my bladder and/or bowel function, e.g. occasional 'accidents', or severe constipation or diarrhoea.
4 ( ) I have serious problems with my bladder and/or bowel function, e.g. routine 'accidents', or need of catheterization or enemas.
5 ( ) I have no control over my bladder and/or bowel function.

Question 9. Usual activities
1 ( ) I am able to perform my usual activities (e.g. employment, studying, housework, free-time activities) without difficulty.
2 ( ) I am able to perform my usual activities slightly less effectively or with minor difficulty.
3 ( ) I am able to perform my usual activities much less effectively, with considerable difficulty, or not completely.
4 ( ) I can only manage a small proportion of my previously usual activities.
5 ( ) I am unable to manage any of my previously usual activities.

Question 10. Mental function
1 ( ) I am able to think clearly and logically, and my memory functions well.
2 ( ) I have slight difficulties in thinking clearly and logically, or my memory sometimes fails me.
3 ( ) I have marked difficulties in thinking clearly and logically, or my memory is somewhat impaired.
4 ( ) I have great difficulties in thinking clearly and logically, or my memory is seriously impaired.
5 ( ) I am permanently confused and disoriented in place and time.

Question 11. Discomfort and symptoms
1 ( ) I have no physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
2 ( ) I have mild physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
3 ( ) I have marked physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
4 ( ) I have severe physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
5 ( ) I have unbearable physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.

Question 12. Depression
1 ( ) I do not feel at all sad, melancholic or depressed.
2 ( ) I feel slightly sad, melancholic or depressed.
3 ( ) I feel moderately sad, melancholic or depressed.
4 ( ) I feel very sad, melancholic or depressed.
5 ( ) I feel extremely sad, melancholic or depressed.

Question 13. Distress
1 ( ) I do not feel at all anxious, stressed or nervous.
2 ( ) I feel slightly anxious, stressed or nervous.
3 ( ) I feel moderately anxious, stressed or nervous.
4 ( ) I feel very anxious, stressed or nervous.
5 ( ) I feel extremely anxious, stressed or nervous.

Question 14. Vitality
1 ( ) I feel healthy and energetic.
2 ( ) I feel slightly weary, tired or feeble.
3 ( ) I feel moderately weary, tired or feeble.
4 ( ) I feel very weary, tired or feeble, almost exhausted.
5 ( ) I feel extremely weary, tired or feeble, totally exhausted.

Question 15. Sexual activity
1 ( ) My state of health has no adverse effect on my sexual activity.
2 ( ) My state of health has a slight effect on my sexual activity.
3 ( ) My state of health has a considerable effect on my sexual activity.
4 ( ) My state of health makes sexual activity almost impossible.
5 ( ) My state of health makes sexual activity impossible.

Appendix 4. Questionnaire of the use of health care services, study V

Please fill out this questionnaire concerning the use of health care services **during the last 3 months**. Mark 0 to the place _____ times/day if you have not visited that particular place or have not been off from work/studies/school. Mark only separate visits on the questionnaire (for example, if you have visited both the doctor's and nurse's receptions at the same time, mark only the doctor's visit).

During the last 3 months, how many times have you visited the following places because of your salivary gland disorder?

1. the health center of the doctor's reception? _____ times

2. the occupational physician's reception? _____ times

3. the nurse's reception? _____ times

4. the separate laboratory tests? _____ times

5. the hospital policlinic? _____ times

6. the hospital emergency policlinic? _____ times

7. the private doctor's reception? _____ times

8. the private otorhinolaryngologist's reception? _____ times

9. **During the last 3 months**, how many times have you made **a phone call** to the nurse or doctor because of your salivary gland disorder? _____ times

10. **During the last 3 months**, how many times have you visited a doctor because of some reason other than your salivary gland disorder? _____ times

11. How many days have you been off work/studies/school **during the last 3 months** because of your salivary gland disorder? _____ days

12. How many days have you been in hospital treatment **during the last 3 months** because of your salivary gland disorder? _____ days